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Review

Bone marrow and peripheral blood stem cell transplantation for malignancy

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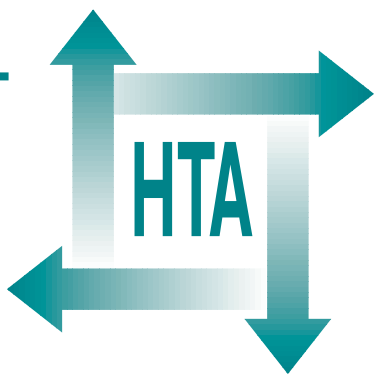
Health Technology Assessment
NHS R&D HTA Programme



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Bone marrow and peripheral blood stem cell transplantation for malignancy

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This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Acute Sector Panel.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will, in England, be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

Series Editors: Andrew Stevens, Ruairidh Milne and Ken Stein
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Contents

List of abbreviations

ABMT	autologous bone marrow transplant*
AlBMT	allogeneic bone marrow transplant*
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
ASCT	autologous stem cell transplant*
BMT	bone marrow transplantation
C	consolidation*
CC	conventional chemotherapy
CCT	controlled clinical trials
CEA	cost-effectiveness analysis*
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
CR	complete remission*
CUA	cost–utility analysis*
DFS	disease-free survival*
EBMT	European Bone Marrow Transplantation Group
EI	early intensification*
EORTC	European Organization for Research and Treatment of Cancer*
GCSF	granulocyte colony stimulating factor*
GMCSF	granulocyte-macrophage colony stimulating factor
GVHD	graft versus host disease
GVL	graft versus leukaemia
HD	Hodgkin's disease
HDT	high-dose therapy
HLA	human leukocyte antigen*
HR	hazard ratio*
I	intensification*
IGCCCG	International Germ Cell Cancer Collaborative Group*
Int	intermediate*
ITT	intention to treat*
ITU	intensive therapy unit*
LI	late intensification*
LRT	log rank test*
LYG	life-year gained*
LYS	life-year saved*
M	maintenance*
MAL	meta-analyses of the published literature*
MAP	meta-analyses of individual patient data*
MRC	Medical Research Council
MUD	matched unrelated donor
NFT	no further treatment*
NHL	non-Hodgkin's lymphoma
NS	not significant*
NSGCT	non-seminomatous germ-cell tumour*
NYR	not yet reached*
OR	odds ratio
OS	overall survival*
PBPC	peripheral blood progenitor cells
PBPCT	peripheral blood progenitor cell transplantation
PC	prospective cohort study*
PCI	prophylactic cranial irradiation*
PCT	progenitor cell transplantation
PDQ	Physicians Data Query*
PFS	progression-free survival
PH	prospective study (comparison with historical controls)*
PPP	purchasing power parities*
QALY	quality adjusted life-year*
QoL	quality of life*
R	retrospective study*
RCo	retrospective study (comparison with concurrent controls)*
RCT	randomised controlled trial
RR	relative risk*
RT	radiotherapy*
TBI	total body irradiation
TTE	time to engraftment*
WF	working formulation*

* Used only in tables and appendices

continued

continued

Abbreviations of drug names*

ACR	actinomyocin-D	DMS	dexamethasone	MP	mercaptopurine
ADR	doxorubicin	DNM	daunomycin	MPRED	methylprenisolone
AMSA	amsacrine	DNR	daunorubicin	NM	meclorethamine
ANC	anthracycline	ELD	eldisin	PCZ	procarbazine
ASP	asparginase	EPI	epirubicin	PRED	prednisolone
BCNU	carmustine	ETOP	etoposide	TMX	tamoxifen
BLM	bleomycin	FLM	fluoxymesterone	TENI	tenopiside
BU	busulphan	FU	fluorouracil	TG	thioguanine
CACP	cisplatin	HU	hydroxyurea	TSPA	thiotepa
CBDSA	carboplatin	IDA	idarubicin	TXL	paclitaxel
CF	calcium leukovorin	IFOS	ifosphamide	VBL	vinblastine
CHL	chlorambucil	L-PAM	melphalan	VCR	vincristine
CTX	cyclophosphamide	MTOX	mitoxantrone		
CYT	cytarbine	MTX	methotrexate	* Used in tables	

Executive summary

Objectives

- To assess the relative effectiveness of high-dose myeloablative therapy and progenitor cell transplantation (HDT/PCT) compared with conventional therapy for the treatment of malignancy.
- To assess the relative cost of HDT/PCT versus conventional chemotherapy (CC).
- To assess the efficacy and cost of bone marrow transplantation (BMT) versus peripheral blood progenitor cells transplantation (PBPCT).

Methods

A systematic review of the published literature was performed.

Malignancies included

Acute myeloid leukaemia (AML), acute lymphoblastic leukaemia, chronic myeloid and chronic lymphocytic leukaemia, malignant lymphoma, multiple myeloma, and breast, ovarian, lung and testicular cancer.

Study selection

No language restrictions were imposed. Studies were eligible if they:

- compared HDT/PCT with CC in the above malignancies with regard to survival and/or progression-free survival (PFS) (comparison could be at any stage of therapy)
- reported an economic evaluation of HDT/PCT compared with CC, or of the use of BMT versus PBPCT
- compared the long-term (> 100 days) toxic effects of HDT/PCT with those of CC
- reported the use of cord blood as a source of progenitor cells.

Data sources

Published studies were identified using electronic literature searches of Cancerlit, Embase, Medline and the NHS Economic Evaluation Database (searches up to and including 31 January 1997). A second search for randomised controlled trials (RCTs) was completed on 1 June 1997. These searches were supplemented by handsearching of conference proceedings of the American Society of Haematology (1992–1996), European Bone Marrow Transplantation Group (1992–1997), the International Society for Experimental Hematology (1992–1996) and the European Haematology Association (1994–1996). In addition, the UK Coordinating Committee on Cancer Research Cancer Trials Register and the National Cancer Institute PDQ database were searched for reports of eligible ongoing and unpublished trials, although no additional information was sought from these studies.

Data extraction was performed independently by two reviewers.

Data synthesis

Quantitative analysis was performed on data from RCTs and controlled clinical trials (CCTs) only. No comment was made on the results of the cohort studies. For economic analyses, costs were converted into 1993 US$ using purchasing power parities published by the OCED and the US All Goods Consumer Price Index published by the Bureau of Labor Statistics.

Results

Studies identified

- Twenty-six RCTs comparing HDT/autologous transplantation with CC and 23 CCTs comparing HDT/allogeneic transplantation with CC (the majority of these were in haematological malignancies).
- Five RCTs comparing BMT with PBPCT.
- Fifteen studies comparing the cost of HDT with that of CC (four using data from RCTs or CCTs).
- Fourteen studies comparing the cost of BMT with PBPCT (two using data from RCTs).

Results of clinical efficacy studies

HDT with autologous transplantation

For the majority of disease sites investigated few RCTs were identified. Those that were identified were generally too small to detect moderate survival differences and poor data reporting restricted quantitative synthesis. In multiple myeloma and adult AML in first remission, fixed time-point analysis perhaps suggested possible improvements in PFS following HDT/autologous transplantation, and in childhood AML the results may suggest a survival benefit for CC. It must be stressed, however, that in no disease site was there sufficient reliable

evidence, that it was not possible to include all identified trials in the analyses, and that fixed time-point analysis is not the most informative means of summarising time-to-event data. Therefore at present there is insufficient reliable evidence to determine whether HDT with autologous transplantation is of benefit in the treatment of any of the malignancies studied.

HDT with allogeneic transplantation

No RCTs comparing HDT/allogeneic transplantation with CC were identified. All prospective trials determined the allocation of treatment on the basis of the availability of an appropriate sibling donor. There are many biases associated with non-randomised trials and as only the published reports were available to this review, we were unable to determine the validity of the treatment allocation process and therefore the reliability of the results. For the majority of leukaemic conditions there were insufficient trials, including insufficient patients, to be able to determine whether HDT with allogeneic transplantation is of benefit. However, in childhood AML in first remission, there is perhaps some suggestion from pooled results of four trials (1017 patients analysed) that there may be a PFS benefit. However, due to incomplete data reporting it is not possible to determine whether there is an overall survival benefit.

BMT versus PBPCT

The five randomised studies identified differed in their administration of granulocyte colony stimulating factor. However the results suggest that the use of growth factor-primed progenitor cell transplants results in faster engraftment than bone marrow harvested without growth factor priming. There was no evidence of a difference in PFS or overall survival between the two sources of progenitor cells.

Economic analyses

Most comparisons of HDT/PCT with CC considered only the costs of the procedure. The use of HDT/PCT was found to cost 1–2 times that of CC in the treatment of acute leukaemia. In other malignancies HDT was 1–4 times the cost of CC. No cost effectiveness analysis was possible.

The use of BMT was found to be approximately 1–1.7 times the cost of PBPCT.

Cord-blood transplantation

Several reports of single transplantation and case series have been published. The initial successes of transplanting patients with cord blood has led to the establishment of cord-blood banks both in Europe and the USA. The efficacy of cord blood as a source of progenitor cells has yet to be tested in a randomised fashion and its use poses several controversial ethical issues.

Long-term toxicities

Very little data were available to compare the long-term toxic effects of HDT/PCT and CC.

Conclusions

As a whole the review has found no conclusive evidence that HDT/PCT is superior to conventional treatment in terms of survival or PFS. Conversely, it has not demonstrated that it is inferior. Given the overall pattern of results, HDT/PCT appears to be a therapy worthy of further exploration.

As few prospective economic analyses were identified it is not possible accurately to determine the comparative cost of HDT/PCT and CC.

Implications for clinical practice

- If sufficient reliable evidence of the comparative benefits of HDT/PCT and CC is to be gathered, then ideal clinical practice should be to consider all patients for whom transplantation is a treatment option for entry into an RCT or CCT.
- In some disease areas the use of HDT/PCT has become adopted as standard therapy on the basis of very limited evidence. These include intermediate-grade non-Hodgkin's lymphoma in second remission, recurrent Hodgkin's disease, and chronic phase myeloid leukaemia. In view of this, RCTs could be difficult to conduct in these areas.
- There is currently insufficient evidence to support the introduction of cord-blood transplantation into routine clinical practice without prospective randomised evaluation.

Research recommendations

- In some disease areas there are a number of on-going trials which should be supported. In other disease areas there is an urgent need for high-quality trials aiming to randomise enough patients to give sufficient power to detect moderate differences in outcome.
- RCTs and CCTs should include long-term follow-up, particularly for trials involving a young patient population in which long-term toxicity is an issue.
- Prospective health economic assessments, ideally using data from RCTs and CCTs, are necessary for each disease area and stage.
- More complete reporting of trials is necessary so that clinical judgements can be based on all of the available results of a trial.

Chapter 1
Introduction

More than 30 years ago it was discovered that bone marrow destroyed by intensive chemotherapy could be successfully replaced by healthy marrow from another individual. This approach was seen to have potential uses in several settings including the treatment of bone marrow disorders and solid tumours. In the treatment of bone marrow diseases, both inborn (e.g. enzyme deficiencies) and acquired (e.g. leukaemia), the aim of transplantation is replacement of defective marrow cells. In the treatment of other malignancies, where it is proposed that more intensive chemo- and radiotherapy regimens may have an increased cytotoxic effect on malignant cells, bone marrow transplantation (BMT) is used to overcome the acute myelotoxicity and associated risk of lethal infection and bleeding.

Because of the toxicity of high-dose therapy (HDT) and BMT this approach has traditionally been used only for treatment with curative intent. However, with increased experience and better control of toxicity, it is becoming more commonly used in the treatment of less chemo-sensitive tumours, either for metastatic disease or in the adjuvant setting where the risks of therapy were previously thought to outweigh the potential benefits.

Progenitor cell transplantation

BMT, or more accurately progenitor cell transplantation (PCT), initially involves – before HTD – the collection of precursor haematopoietic progenitor cells (stem cells) from either a healthy human leukocyte antigen-matched sibling or an unrelated donor with the appropriate tissue type (allogeneic transplantation), or from the patient themselves (autologous transplantation). On completion of treatment stored stem cells are re-infused into the patient, whereupon they migrate to the bone marrow to aid haematopoetic recovery and 'rescue' the patient from lethal myelotoxicity.

In the context of this report HDT/PCT is considered to mean the myeloablative chemo- and radiotherapy treatments together with PCT.

Allogeneic transplantation, which has been largely restricted to the treatment of leukaemias, generally uses marrow from matched sibling donors. This type of transplant may have a therapeutic benefit beyond aiding haematopoetic recovery, as the transplanted cells exert an immunological effect on the leukaemia. The treatment, however, may also invoke graft versus host disease (GVHD), a condition in which the infused cells recognise the patient as foreign and establish a hostile immune response. Not all patients will have a suitable sibling donor, so at present allogeneic transplantation has limited applicability. However, with an increasing ability to prevent and manage GVHD and the use of tissue-type matched unrelated donors (MUDs), the potential uses for allogeneic transplantation are increasing, although the toxicity of MUD transplantation is still higher than that of sibling transplantation. In contrast, since autologous transplantation utilises a patient's own cells, it is more widely applicable and not liable to give rise to GVHD. Autologous rescue has been used as part of the treatment of patients with a variety of malignancies.

There are two major sources of stem cells: the bone marrow where they are produced, and the peripheral blood. Under normal circumstances, the concentration of stem cells in the general circulation is low; however their numbers can be greatly increased following the administration of growth factors with or without chemotherapy. Harvesting stem cells from the peripheral blood as opposed to the bone marrow has potential advantages; the procedures for collection are less invasive and the time to haematopoetic recovery is generally thought to be decreased, which could result in a reduction in hospitalisation and possibly in costs.

Benefits and risks

As for any treatment, the potential benefits of HDT/PCT must be balanced against serious potential risks. In some illnesses HDT/PCT may offer an increased chance of cure or at least prolonged survival time. However, in other diseases, even if transplantation offered only equivalent survival time, a shorter treatment duration may be a major advantage. For example, the conventional treatment for acute lymphoblastic leukaemia

(ALL) in second remission normally lasts up to 2 years whereas HDT with autologous BMT lasts only 3 months. Decreasing treatment time may improve a patient's quality of life and reduce costs. Similarly, HDT/PCT could increase the duration of progression-free survival (PFS) without affecting overall survival but thereby reducing the number of treatments a patient requires.

It is thought that PCT, especially allogeneic transplantation, may be associated with higher treatment-related morbidity and mortality than conventional chemotherapy (CC). It is also possible that patients receiving HDT/PCT are at greater risk of long-term toxicities than patients who are treated with CC. Long-term toxicities which have been associated with HDT/PCT include secondary cancers, serious cardiac and pulmonary complications, cataracts, gonadal and other hormonal dysfunction, and psychological problems, many of which have also been linked to the administration of conventional dose chemotherapy.

Cost and cost-effectiveness

HDT/PCT is generally considered to be an expensive procedure, and while this may be true of the cost of initial treatment there is no reliable evidence as to the comparative costs, when set against conventional therapy, if an evaluation accounts for long-term events.

The extra initial cost of HDT/PCT in comparison with conventional therapy comes mainly from progenitor cell harvesting and processing, blood products used, and antimicrobial support, together with increased hospitalisation, as treatment is given almost exclusively on an inpatient basis. Allogeneic transplantation is thought to cost more than autologous transplantation because of additional expenses including tissue typing and immunosuppressive regimens. However, if HDT/PCT cures a greater percentage of patients, then the cost of treating relapses will be reduced; if the difference in the cure rates is large, then HDT/PCT could become the more economically favourable treatment. In contrast, if the incidence of long-term toxicities is high, the full cost of HDT/PCT is likely to become much greater than that of conventional therapy.

Current status

As the potential applications of HDT/PCT increase so do the number of procedures performed. The European Bone Marrow Transplantation Group (EBMT), who have published guidelines on the use of HDT/PCT[1] (see appendix 5), estimated that less than 200 transplants were performed in Europe in 1980,[2] with this figure rising to over 12,000 in 1994.[3] Previously the greatest transplantation activity was in the haematological malignancies; however the use of HDT/PCT is now increasing in the management of solid tumours both for metastatic disease and as adjuvant treatment after surgery.

The current use and application of HDT/PCT varies widely between diseases. For some conditions, such as chronic myeloid leukaemia (CML), results with CC are considered to be so poor that allogeneic transplantation has become standard practice. In other conditions, for example lung and ovarian cancer, the process is still considered relatively experimental.

The introduction of HDT/PCT into medical practice has taken place largely on the basis of information from case series and cohort studies and few randomised controlled trials (RCTs) have been conducted. Establishment of the advantages and disadvantages of HDT with either autologous or allogeneic rescue therefore requires more reliable evidence from RCTs and systematic synthesis of that information.

New approaches

With HDT becoming increasingly common, new technologies and approaches are being investigated in an attempt to increase efficacy and applicability, and to reduce long-term complications and toxicities. One important area of research is the identification of those patients who are most at risk of failure on conventional therapy, whose condition may warrant intensive treatment. Conversely, it is also necessary to identify patients least at risk who may be cured by CC. It has not proved straightforward to identify reliable risk factors, especially in some haematological malignancies, but progress in these areas may come from advances in the understanding of the cellular pathogenesis of malignancy and the development of prognostic factor indices from large patient registries, coupled with appropriate RCTs. In these ways, in the future it may be possible to identify groups of patients who are likely to benefit most from HDT/PCT.

Autologous transplantation carries a small risk that stem cells re-infused following myeloablative

therapy are contaminated by malignant cells removed from the patient during harvesting which may cause future relapse. Techniques have been developed which aim to reduce this possibility by either removing unwanted cells or positively selecting stem cells (purging), but as yet there are no results from RCTs to establish the efficacy of this approach.

To improve the availability of MUD grafts for allogeneic transplantation, the use of umbilical cord blood harvested from the placenta following birth is being investigated as an alternative source of stem cells. The naïve immune repertoire of the neonatal system may pose a lesser risk of GVHD than other allogeneic transplantations and the method of collection avoids invasive procedures. The feasibility and cost of collection and storage of cord blood have yet to be fully assessed.

Systematic review

Although there are several thousand papers and abstracts reporting the results of PCT series, there is still great uncertainty as to the true effectiveness of HDT/PCT. This review has therefore been undertaken to assess the published evidence for the efficacy of HDT/PCT compared with conventional therapy in a variety of malignancies.

The best evidence of the effectiveness of healthcare interventions comes from the results of RCTs and the biases associated with non-randomised studies are well established.[4] To avoid bias and to maximise reliability, systematic reviews are usually restricted to evidence from RCTs. For most disease areas considered, that approach has been applied in the present review, with quantitative analysis restricted to the results of RCTs.

No RCT was identified that compared the efficacy of allogeneic transplantation with that of conventional therapy, owing to the recognised difficulties of carrying out RCTs for allogeneic transplantation. Therefore, for leukaemia (the only disease site for which allogeneic transplantation is commonly used) the findings of pseudo-randomised controlled clinical trials (CCTs), in which the use of allogeneic transplantation is determined by the availability of a matched sibling marrow donor, have been assessed and analysed. No CCTs of allogeneic transplantation were identified for any other disease sites. The results of these CCTs must be considered in the light of the potential problems associated with their methodology.

This systematic review aimed to identify all relevant published studies of HDT/PCT, appraise the currently available evidence, and provide an objective and comprehensive summary of that evidence. As in any rapidly evolving field, new evidence is continually emerging. This is especially true of HDT/PCT in which for many diseases there are more patients included in on-going trials than in all published RCTs.

The present review has, as far as possible, identified on-going and recently closed trials and it is recommended that the conclusions are considered in conjunction with the results of these RCTs when they are published.

Chapter 2
Methods

Introduction

This review investigated the effectiveness of HDT/PCT compared with CC in malignant lymphoma (non-Hodgkin's lymphoma and Hodgkin's disease), multiple myeloma, leukaemia (acute and chronic), germ-cell tumours and in breast, ovarian and lung cancer. These disease sites were chosen as they represent the areas in which most transplantation activity has been focused in the past and in which, owing to the incidence of the disease, the clinical and economic impact is likely to be greatest. The review also assessed the literature relating to the cost-effectiveness and long-term toxicity of HDT/PCT compared with CC, and the literature concerning the use of cord blood. In addition, RCTs comparing BMT and peripheral blood progenitor cell transplantation (PBPCT) were reviewed.

Given the limited time that was available, the review is based on the published literature only and no results from unpublished trials are included. It is therefore possible that the review suffers from publication bias,[5] whereby the results of positive trials are more likely to appear in print than those of negative or inconclusive trials.

The methodology used was pre-specified in the systematic review protocol, which is reproduced in appendix 1.

Study identification

Studies were identified by searching the following electronic databases up to and including 31 January 1997:

- Medline
- Embase
- Cancerlit
- Cochrane Controlled Trials Register
- NHS Economic Evaluation Database.

Medline, Embase and Cancerlit were re-searched for RCTs on 1 June 1997 to identify any RCTs that may have been indexed between January and June. RCTs were also identified by searching the UKCCCR Trials Register, Center Watch Clinical Trials Listings, and the Physicians Data Query (PDQ) database (see appendix 4). Planned searches of the Science Citation Index and Biossis were not done because preliminary investigations found that they yielded no additional useful information. All journals that were *a priori* deemed by the clinical coordinators to be potentially important sources of relevant publications are indexed on one or more of the electronic databases searched. Therefore, although it is recognised that bibliographic tagging and indexing are not always comprehensive,[6] no handsearching of journals was performed.

Conference proceedings of the following organisations were handsearched for RCTs and CCTs and also for abstracts relating to use of cord blood, long-term toxicity, and cost-effectiveness:

- European Haematology Association (1994–1996)
- EBMT (1992–1997)
- American Society of Hematology (1992–1996)
- International Society for Experimental Hematology (1992–1996).

The 1997 proceedings of the EBMT were also handsearched to identify more recent RCTs and CCTs.

Electronic databases were searched using a slightly modified version of the Cochrane Collaboration strategy for identifying RCTs,[6] together with more general strategies which aimed to be comprehensive and identify non-randomised comparative studies and papers relating to the use of cord blood, long-term toxicity, and cost-effectiveness. These search strategies were listed in the systematic review protocol (see appendix 1).

Eligibility criteria

Studies investigating the efficacy of HDT/PCT

Studies investigating the efficacy of HDT/PCT were eligible for inclusion in the review provided that the authors stated that HDT was administered

(no judgement was made by the reviewer as to whether the HDT was truly myeloablative) and the patients were intended to receive PCT. The study must also have investigated survival and/or PFS and included a conventional therapy comparator arm. PFS was defined as patients alive and progression-free at time of analysis. RCTs which did not report on these end-points but which were otherwise eligible for the review are listed in appendix 2.

Economic evaluation studies

All studies that made an economic evaluation of HDT/PCT compared with CC and/or those that calculated the cost of administering HDT/PCT in the UK were included. In addition, all studies that compared the economics of the use of BMT with that of PBPCT were also included.

Studies investigating the use of cord-blood transplantation

All publications in which the authors stated that cord blood was used as a source of progenitor cells for use in conjunction with HDT in humans were reviewed.

Studies investigating long-term toxic effects

All papers in which the authors stated they were comparing long-term (> 100 days) toxic effects of HDT/PCT and a control CC population were included.

Trials comparing BMT with PBPCT

All trials that randomised the type of haematological support (either bone marrow or peripheral blood progenitor cells [PBPCs]) which patients were to receive following HDT were included.

End-points

The end-points of survival and PFS were chosen because they provide the most clinically relevant measures of a treatment's efficacy in these diseases.

PFS is the time a patient remains alive and free from worsening disease. In the treatment of many malignancies, PFS is an important end-point: the longer a patient can remain progression-free, the less treatment they require. If the effectiveness, in terms of survival, of two treatments were equivalent it would usually be preferable to treat patients with the therapy that gave the longest PFS.

Classification of studies

Studies comparing the efficacy of HDT/PCT with CC were classified as follows:

- prospective RCTs
- prospective CCTs with pseudo-randomisation (e.g. transplantation given to all patients who had a matched sibling donor)
- prospective cohort studies with a non-randomised comparator (including matched controls from a national/international registry and historical controls)
- retrospective cohort studies with non-randomised comparators.

For each disease site a decision, based on the number of trials, patients and events, but without knowledge of the results, was made as to which level of evidence should be considered. If sufficient evidence was available from the RCTs then no other studies were reviewed. Similarly, if sufficient evidence was available from the RCTs plus CCTs then no further studies were reviewed. Otherwise all the above categories of study were included, but no conclusions were drawn from cohort studies. No case series were included.

Data extraction

For each disease site, all titles identified by search strategies were assessed for relevance by one reviewer and a random sample of 10% of the titles was assessed by a second reviewer to check for consistency and completeness. Abstracts were downloaded for titles judged to be potentially relevant and then full publications were obtained for all abstracts that indicated potentially relevant studies. (Full papers were also obtained when the abstract did not give a clear indication of the relevance of the study.) All eligible publications were reviewed by at least one clinical and one non-clinical reviewer. Data were extracted using data extraction sheets (see appendix 1). Discrepancies were resolved by discussion and by seeking a third opinion when necessary. When studies generated multiple publications the most recent paper containing sufficient information was used for data extraction and earlier full publications were cross-referenced.

Analyses

Quantitative analyses were performed only for RCTs and CCTs. Information on cohort studies

was included in tables, but owing to the well-known problems associated with such studies no data synthesis was attempted. It was stated in the review protocol that the published results of RCTs would be analysed and statistically combined by calculating hazard ratios either based on summary statistical information[7] or estimated from a series of points on survival curves. However, the former proved impossible because statistical reporting was incomplete and of a generally poor standard, and the latter was impossible because many papers did not present survival curves. Therefore, odds ratios (ORs) were calculated at one or more time-points for each disease site and end-point. The time-points used were selected according to clinical importance and the maturity and availability of data presented. The observed and expected number of events were either read from the publication or calculated from curves. These were then used to calculate ORs for individual trials and combined using the Peto method according to the fixed effect model.[8] Ideally, the number of patients and events included in these calculations should have been adjusted to account for immature data.[7,9] However, the information required to make such adjustments was presented in so few trial reports that adjustment was impractical. Medical Research Council (MRC) Cancer Trials Office in-house software was used to perform the statistical analyses and produce the OR plots.

Where trials with multiple CC arms presented individual analyses of HDT/PCT versus each chemotherapy arm, these are given in the summary tables. However, for the combined analysis, the numbers of events on each of the CC arms were summated to a single value, giving the number of events on treatment compared with control. To do otherwise would essentially mean multiple counting and including the HDT/PCT patients more than once.

Chi-square tests for heterogeneity[10] were used to test for gross statistical heterogeneity between individual trials, and chi-square tests for interaction were used to test for gross statistical heterogeneity between groups of trials. Unless otherwise stated all *p* values are on 1 degree of freedom.

Explanation of presentation of results

In discussing the results of individual trials, most emphasis is placed on the survival results reported for the log rank test, where available. This is because these are time to event analyses (from which a hazard ratio could be calculated if sufficient information was presented), giving an overall summary of the entire survival experience. If such information was not reported, the ORs which were calculated at specific points in time are discussed. It is possible that these ORs may not always be consistent with the overall conclusions of an individual trial as the calculations account for only the total number of events at a particular point in time and do not account for time to event or the shape of a survival curve. This may be a particular problem if ORs are calculated at points of maximal or minimal curve divergence or in cases in which the survival curves cross.[9] For the reasons stated above, the results of individual trials were combined to produce pooled ORs at specific time-points and it is these that are discussed in terms of estimates of overall effect.

Explanation of tables

Tables of studies included in the review are presented separately for RCTs, for CCTs and for other comparative studies.

The years of patient entry are presented along with brief details of the treatment regimens used in studies of solid tumours, lymphoma and myeloma. For leukaemia, details of the type of therapy used are listed, but individual chemotherapy regimens are not presented, as standard accepted regimens are both long and complex. The drug abbreviations used in the tables are listed on page ii.

For RCTs and CCTs, median survival and PFS are listed as well as percentages at chosen time-points. Unless otherwise stated, quoted rates are estimates given in the text or read from Kaplan-Meier curves. Reported summary statistics relating to these end-points are presented (unless stated otherwise these refer to the results of the log rank test), as are ORs calculated for the review. Owing to the unreliability of other types of study no reported statistics or calculations are presented. For the end-point of PFS, progression or death is counted as an event and this information is presented only for those trials that define the end-point in this way.

The comments column gives further explanation of the data when necessary, highlights any potential problems or notable features of the study design, and presents a brief indication of the authors' conclusions for RCTs.

Explanation of plots

The OR for each trial is represented by the central square on each bar, the size of which is directly proportional to the amount of information available in the trial. The outer limits of the bar represent the 99% confidence interval (CI) and the inner tick marks show the 95% CI. The vertical line drawn through the OR value of 1.0 indicates no difference between the two treatment arms. An OR lying to the left of this line, with an OR < 1.0, suggests an advantage to HDT/PCT whereas an OR lying to the right of the line, with an OR > 1.0, suggests a benefit to CC. If a CI crosses this line, then the result for that trial did not reach significance at conventional levels. The diamond shown below a group of trials represents the combined result for those trials. The diamond is centred on the combined OR estimate and the edges of the diamond indicate the 95% CI.

Data included

Search strategies identified almost 14,000 potentially eligible titles from which 1301 potentially eligible abstracts were identified. After reviewing all of the abstracts, 566 publications were deemed potentially relevant and were reviewed in full (see *Table 1*). Ultimately 26 RCTs, 22 CCTs and 48 other studies were included in this systematic review of the efficacy of HDT/PCT.

For acute myeloid leukaemia (AML) the review was restricted to RCTs/CCTs. For all other disease sites, comparative cohort studies were also reviewed. A total of 3479 patients (who received either HDT/PCT or CC) were included in RCTs, more than 2500 patients were included in CCTs, and 9008 patients who received HDT/PCT were included as part of other non-randomised studies.

TABLE 1 *The numbers of titles, abstracts and papers reviewed*

Disease site	Titles reviewed	Abstracts reviewed	Papers reviewed
Breast	1893	134	68
Lung	971	78	39
Testicular	251	251	30
Ovarian	117	117	35
Lymphoma + myeloma	5563	371	189
Leukaemia	5167	350	205
Total	**13,962**	**1301**	**566**

Chapter 3

Introduction to acute leukaemia trials

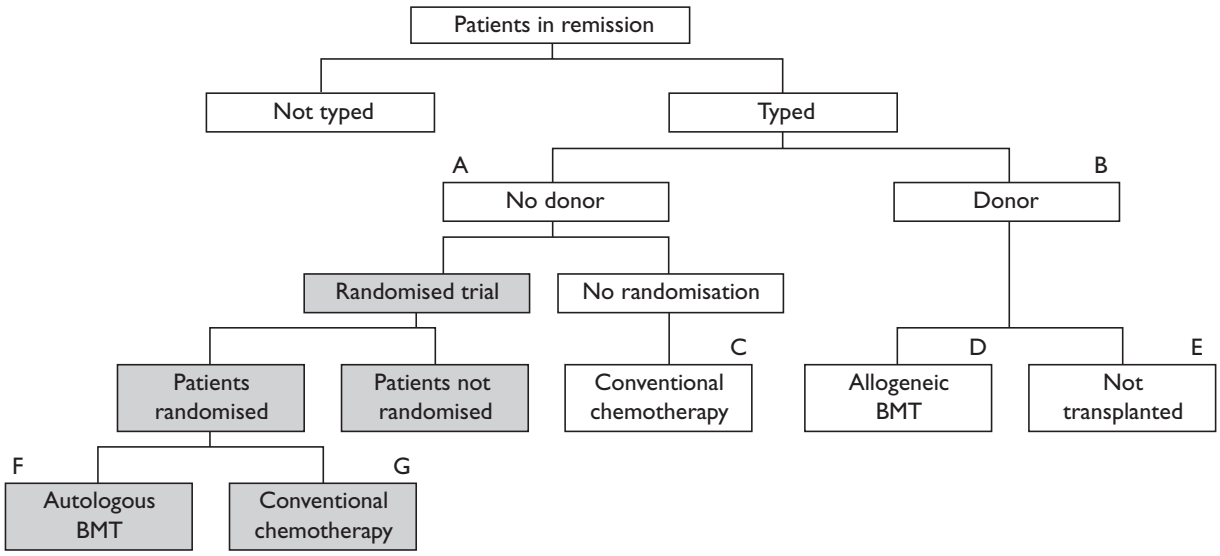
It is in the treatment of acute leukaemia that HDT with autologous or allogeneic transplantation has been pioneered. Sibling allografting, where available, may be used preferentially because the donor cells themselves are thought to have an immunological effect against the tumour – a graft versus leukaemia (GVL) effect – and there is a very low possibility of cancer cells being re-infused. Sibling allogeneic transplants are not widely applicable owing to small family sizes in the developed world and there being only a 1 in 4 chance that a potential sibling donor will have immunologically compatible marrow. In addition, transplant-related mortality increases with age because of the increasing morbidity associated with GVHD. To increase the number of available donors, stem cells from MUDs have been tested. The mortality and morbidity associated with this process are higher than with sibling grafts and it remains an experimental procedure.

As with all therapies the most reliable evidence of a treatment's relative efficacy comes from the results of RCTs. For autologous transplantation the conduct of such trials is relatively straightforward. However, it is more difficult to perform RCTs for sibling allogeneic transplantation because not all patients will have an appropriate donor. Prospective trials that have attempted to determine the effectiveness of sibling allogeneic transplantation have allocated treatment on the basis of donor availability. Although this process is sometimes termed 'genetic randomisation', there are many biases associated with this way of allocating treatment. Not least, patients who are known to have a compatible sibling donor are often compared with all other patients regardless of whether their marrow was sent for genetic typing. In interpreting the results of such trials (CCTs) it is important to consider the shortcomings of this design (*Figure 1*). As described in chapter 2, the results of RCTs are presented separately from those of CCTs.

For trials which include both a true randomised comparison of autologous PCT versus CC and a comparison of sibling allogeneic PCT versus CC, results of the autologous transplantation versus CC randomisation are presented in an RCT table. The results of the allogeneic transplant versus CC comparison appear in a table of cohort studies. It is inappropriate to perform any data synthesis on the comparison of a cohort of patients randomised to receive CC with a cohort of patients with a sibling donor, as it is likely that the CC arm will contain a more select group of patients. This is because patients with a sibling donor are likely to have been selected at an early stage as they will possibly have had tissue typing early in induction, whereas those randomised to CC will have completed induction therapy and have been judged fit enough to undergo randomisation (*Figure 1*).

Because the treatment of acute leukaemia is generally standardised across centres, the approach used to conduct most controlled trials is similar. Following induction treatment, patients in remission are given additional therapy to consolidate their response. Patients with a compatible sibling donor (B) undergo HDT with allogeneic BMT. All other patients receive conventional therapy. In some trials those patients without a compatible donor are then randomised to receive either conventional consolidation chemotherapy (G) or HDT and an autologous bone marrow transplant (F) (shaded areas in schema).

As with all clinical trials, not all patients will follow the protocol design due to health status, preference or eligibility. When considering the validity of a trial it is important to determine whether these patients have been included appropriately in any analysis (i.e. an intention to treat analysis).



☐ Denotes schema if randomisation between CC and autologous BMT is part of the trial.

RCTs
RCTs comparing autologous transplantation with CC compare the outcome for patients who reach box F with the outcome for patients who reach box G.

CCTs
CCTs investigating the potential benefit of sibling allogeneic transplantation compare the outcome of patients in box B (regardless of whether they actually receive a transplant) with patients in box A.

Cohort studies
It is often unclear from a report of a trial (especially an abstract) whether a study is a CCT or if it is comparing patients who received a transplant (box D) with all the patients who did not receive a transplant (box E), did not have a donor (box A) or did not even get tissue typed.

The comparison of patients who receive CC in a truly randomised part of a trial with patients who have a matched donor allocated allogeneic transplantation (box G versus box D) is considered to be a cohort study as the groups are unlikely to contain comparable patients.

FIGURE 1 *Typical simplified schema for trials comparing HDT including sibling allogeneic or autologous transplantation with CC in acute leukaemia*

Chapter 4

Review: paediatric acute lymphoblastic leukaemia

Introduction

ALL accounts for approximately 80% of all childhood leukaemias.[11] The provision of treatment in the UK is highly organised with the majority of cases being treated in dedicated units in teaching hospitals and almost all patients following MRC trial protocols. Although it is likely that there are a number of distinct disease entities within this overall umbrella, when taken as a whole, CC is highly effective.

Following standard therapy, approximately 95% of patients achieve a first complete remission, and around 70% remain free of disease in the long-term.[11] Treatment is protracted, being given in intensive phases which involve hospitalisation (induction and consolidation) followed by a maintenance phase which is given on an outpatient basis over a 2-year period. Although this treatment is highly successful, it is associated with appreciable morbidity, and expense, and it has therefore been suggested that HDT with autologous transplantation may have a role in consolidating first remission by reducing the total treatment time and potentially improving a patient's quality of life.

For patients whose disease recurs, the outcome is much worse, with about 70% reaching a second remission and up to 30% remaining free of the disease in the long-term.[12,13] At second relapse the outcome is even more unfavourable. This has warranted the testing of both allogeneic and autologous transplantation in patients whose leukaemia is chemosensitive. Preliminary cohort studies of HDT with allogeneic BMT given after relapse have suggested that good outcomes can be obtained using this approach. However there is a significant treatment-related mortality which is higher with unrelated donors than with sibling donors, and there is also a significant long-term morbidity specific to this age group.

There are several other issues to be considered. Although a number of clinical factors can predict high-risk disease, there are no reliable prognostic indices. Thus, a major focus of research is the identification of the one-third of cases that are likely to relapse and are most likely to benefit from HDT/PCT as part of initial treatment. It is also thought that the timing of relapse may be a indicator of survival: relapse while on maintenance therapy is thought to be associated with a very poor outcome, and the further from treatment that relapse occurs the better the outcome. This may warrant the approach of HDT/PCT being targeted at early recurrence.

Methods

The methods set out in chapter 2 were used. No RCTs and two CCTs were identified. Incomplete reporting of trials makes it difficult to categorise studies and it is possible that the CCTs identified were actually cohort studies. Data from other, published, comparative studies were tabulated to provide supplementary qualitative information.

Results

Reports of two CCTs comparing allogeneic transplantation with CC were found. One CCT involved patients in first remission (*Table 2*),[14] and the other involved patients in second remission (*Table 3*).[15] No RCTs were identified. Data from other comparative studies are presented in *Tables 4–7* to provide supplementary qualitative information.

First remission

CCT comparing HDT/allogeneic transplantation with conventional therapy

The one CCT identified which compared HDT/allogeneic transplantation with CC (*Table 2*) registered 111 patients and accrued patients between 1985 and 1990.[14]

Survival

The authors reported no evidence of a difference in survival, although no data were presented to support this statement.

PFS

A PFS curve is presented in the paper. The authors quote an OR of 0.8 (95% CI 0.43–1.14), indicating

that there was no evidence of a difference between the two treatments.

Second remission

CCT comparing HDT/allogeneic transplantation with conventional therapy

The CCT identified included 45 patients accrued between 1976 and 1980.[15] From the information reported in this paper it is unclear whether the study was a CCT or a prospective cohort study. The data presented in *Table 3* should therefore be interpreted with caution.

Survival

The authors presented the numbers of patients alive at the time of analysis which favoured the HDT/PCT arm. However neither summary statistics nor a survival curve were presented and therefore it was not possible to calculate an OR.

PFS

No PFS data were presented and although the authors comment that HDT with allogeneic transplantation offered the best chance of long-term remission, no statistical data were quoted.

Discussion

The use of HDT with allogeneic transplantation has become, for many, the treatment of choice for paediatric patients who relapse and have poor prognostic features. However this treatment strategy is based on the results of cohort studies and not on the findings of more reliable RCTs or CCTs. Two CCTs comparing HDT/allogeneic transplantation with CC were identified, one investigating its use in first remission and one in second remission. The study which involved patients in first remission found no evidence of a statistically significant difference between HDT/allogeneic transplantation and CC. The paper on the trial involving patients in second remission made no statistical comment on the findings and was too poorly reported to allow any data synthesis. Both trials registered very few patients, 111 and 45 respectively, and therefore only large differences in outcome could be reliably detected. It is therefore not possible to comment with any certainty on the true efficacy of HDT/allogeneic transplantation compared with CC for the treatment of paediatric ALL.

The amount of pseudo-randomised evidence comparing HDT/allogeneic transplantation with CC for patients in second remission is somewhat overwhelmed by the literature on the results of potentially unreliable and possibly biased cohort studies. It is important that at relapse patients are entered into well-designed trials, as it is only by adopting this approach that reliable evidence of treatment efficacy and long-term side-effects will become available. Such randomisation may be difficult for clinicians who perceive a treatment benefit for allogeneic transplantation. There is, however, one currently on-going trial and participation in this trial should be supported *(Table 8)*.

No randomised studies were identified which compared HDT/autologous transplantation with CC in either first or second remission, and therefore it is not possible to make any comment on the efficacy of this treatment. There are three on-going or as yet unreported trials and entry into the open trials should be encouraged *(Table 8)*.

The perception that HDT/allogeneic transplantation is of benefit for paediatric patients with ALL in second remission has led investigators to use stem cells from MUDs for patients who do not have a matched sibling donor. The morbidity associated with MUD transplantation is greater than for sibling allografts and whether it confers an advantage over CC is presently being tested in a randomised trial *(Table 8)*.

TABLE 2 *CCT comparing HDT/allogeneic PCT with CC in the consolidation of first remission in paediatric ALL*

Trial reference	Entry years	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Chessells *et al*, 1992[14] (full paper)	1985–90	EI HDT + AIBMT [CTX,TBI]	EI + cranial RT LI M	111	41	70	–	–	NS	–	69:69 2 years 63:54 4 years	NYR:NYR	OR = 0.8 (95% CI 0.43–1.14) p = 0.8	1.01 (0.34–3.00) 2 years 0.69 (0.25–1.92) 4 years	6:4	Only patients tissue typed were included in the analysis. Authors mention that there is no significant survival advantage to allogeneic BMT.

* *See list of abbreviations of drug names on page ii. RT = radiotherapy; TBI = total body irradiation.*

AIBMT = allogeneic bone marrow transplant; EI = early intensification; LI = late intensification; M = maintenance; NYR = not yet reached.

The study reported in this table is not a randomised trial, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 3 *CCT comparing HDT/allogeneic PCT with CC in the consolidation of second and subsequent remission in paediatric ALL*

Trial reference	Entry years	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	Toxic deaths HDT:CC	Comments
Johnson *et al*, 1981[15] (full paper)	1976–80 [CTX,TBI]	HDT + AIBMT	M	45	24	21	46:10[a]	–	–	–	–	–	4:–	It is not clear if all patients were tissue typed or if all patients who had an eligible donor were included in the transplant arm. [a] These are crude, not Kaplan-Meier, survival values for time of analysis; no indication of median survival times was given. The CC group contained more patients with a poor prognosis and the median duration of remission was shorter than that of the HDT group. More extramedullary relapses in the HDT group. Authors conclude that allogeneic BMT offers the best chance of long-term remission.

* *See list of abbreviations of drug names on page ii.*

Superscript letters cross-reference to comments column.

The study reported in this table is not a randomised trial, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 4 *Cohort study comparing HDT/autologous PCT with CC in the consolidation of first remission in paediatric ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Schaison *et al*, 1993[16] (abstract)	1987–91	PC	HDT + ABMT [L-PAM, TBI or CYT, L-PAM, TBI]	–	43	17	26	–	–	20:28 15 years	–	1:1	Marrow purged in nine patients.

* *See list of abbreviations of drug names on page ii.*

ABMT = autologous bone marrow transplant; PC = prospective cohort study.

The study reported in this table is not a randomised trial, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 5 *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of first remission in paediatric ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Schaison *et al*, 1993[16] (abstract)	1987–91	PC	–	–	48	22	26	–	–	58:28 1.5 years	–	1:1	Authors comment that the best treatment is allogeneic BMT, but stress the need for improved CC.
Saarinen *et al*, 1996[17] (full paper)	1981–91	R	HDT + AlBMT [majority CTX + TBI]	CC on various trial protocols	66	22	44	–	–	87:55 2 years 81:50 4 years	NYR:NYR	3:4	Matched pair comparison. Authors comment that BMT is indicated for patients with poor prognosis.

* *See list of abbreviations of drug names on page ii.*

R = retrospective study.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 6 *Cohort studies comparing HDT/autologous PCT with CC in the consolidation of second remission in paediatric ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Uderzo *et al*, 1995[12] (full paper)	1980–89	RCo	HDT + ABMT [CTX (120), TBI (9.9–12 Gy) or CTX, BU]	Multidrug protocol (2 years)	266	36	230	–	–	29:38 2 years 23:23 4 years	17:19	3:6	Review of all patients achieving second CR in participating centres. Cox model applied to the CC data in the PFS curve. Authors make no comment about the ABMT vs. CC comparison but report that patients who were relapsed soon after first-line treatment were less likely to relapse if they received a BMT.
Borgmann *et al*, 1995[18] (full paper)	1983–94	RCo	HDT + ABMT [Majority TBI + ETOP ± CTX]	C + M	104	52	52	–	–	36:47 2 years 26:37 4 years	14.5:19.5	2:1	Matched pair analysis. Patients received uniform chemotherapy as all were treated in multicentre trials. Authors conclude there is no advantage of ABMT over CC.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

C = consolidation; CR = complete remission; RCo = retrospective study of BMT patients compared with concurrent controls.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 7 *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of second remission in paediatric ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Boulad *et al*, 1994[19] (abstract)	1979–91	RCo	HDT + AlBMT [TBI, CTX]	–	88	39	49	–	–	61:30 at time of analysis	–	–	At time of analysis patients in the BMT cohort had longer follow-up than those in the CC cohort. Authors conclude that duration of first relapse had no effect on the relative effect of BMT compared with CC.
Chessells *et al*, 1986[20] (full paper)	1980–84	RCo	C HDT + AlBMT [CTX (120), TBI (9 Gy)]	C M ± LI	53	13	40	–	–	35:42 2 years	11:3	3:2	Paper contains some comparative information on long-term toxicity. Authors state that a higher number of patients on CC had relapsed while still on maintenance therapy, and report that the patients on CC were younger.
Harris *et al*, 1987[21] (full paper)	1980–86												Comparison of two HDT regimens vs. one chemotherapy cohort.
Comparison 1			HDT + AlBMT [CTX, TBI]	M (3 years)	77	25	52	46:32 2 years	–	62:36 2 years	–	–	Authors comment that improved survival is seen in the HDT group receiving CYT.
Comparison 2			HDT + AlBMT [CYT, TBI]	M (3 years)	67	17	52	62:32 2 years	–	36:19 2 years	–	–	
Torres *et al*, 1989[22] (full paper)	1980–88	RCo?	HDT + AlBMT [CTX (120), TBI (9 Gy)]	–	76	21	40	47:22 2 years	18:10.5	59:20	NYR:9	3:0	Excluded 15 patients who relapsed within 3 months of achieving second remission. Authors conclude there are large limitations to AlBMT – new strategies must be investigated.
Uderzo *et al*, 1995[12] (full paper)	1980–89	RCo	HDT + AlBMT [mainly CTX (120), TBI (10–12 Gy) or CTX + BU]	Multidrug protocol (2 years)	287	57	230	–	–	43:38 2 years 41:23 4 years	52:19	11:6	Authors conclude that AlBMT reduced the risk of further relapse but had no effect on survival.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 7 contd *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of second remission in paediatric ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Ringden *et al*, 1989[23] (full paper)	1981–84	RCo	HDT + AlBMT [CTX (120), TBI (10 Gy)]	–	90	22	68	41:25 5 years	–	–	–	–	CC patients must have survived at least 3 months. HDT after the second, third or fourth relapse. For patients who relapsed during initial treatment, HDT is superior; for late relapsers, HDT is inferior.
Hoogerburgge *et al*, 1995[24] (full paper)	1982–91	RCo	HDT + AlBMT [various + TBI]	M	122	25	97	–	–	56:39 2 years 44:24 4 years	26:14	4:0	Matched controls. Authors comment that there were fewer relapses in the HDT arm, but this is balanced by high treatment-related mortality.
Barrett *et al*, 1994[25] (full paper)	1983–91	RCo	HDT + AlBMT	–									Paper reports on two comparisons, one a matched pair analysis, the other a cohort study.
Matched pair comparison					510	255	255	–	–	44:23 2 years 40:19 4 years	16.5:12	–	Patients in the matched cohort were selected from the unmatched cohorts below. HDT cohort taken from a registry.
Unmatched cohort comparison					916	376	540	–	–	42:16 2 years 37:16 4 years	17:10	–	
Frassoni *et al*, 1985[26] (abstract)	–	RCo	HDT + AlBMT [CTX (120), TBI (9.9–12 Gy)]	C + M	31	14	17	47:0 2.5 years	–	50:14 2 years	–	–	This report is from the same institution as reference 27. It is possible that these patients are included in that paper.
Bacigalupo *et al*, 1986[27] (full paper)	–	RCo	HDT + AlBMT [CTX (120), TBI (9.9–12 Gy)]	M	36	17	19	62:35 2 years	–	58:18	–	2:0	Authors state that the relative effectiveness of allogeneic BMT compared with CC is not affected by duration of first remission. It is possible that the patients in reference 26 are included in this paper.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 7 contd *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of second remission in paediatric ALL*

			Treatment regimen*		No. of patients			Survival		PFS			
Trial reference	**Entry years**	**Study type**	**HDT (total dose, mg/m^2)**	**CC**	**Total**	**HDT**	**CC**	**% HDT:CC**	**Median (months) HDT:CC**	**% HDT:CC**	**Median (months) HDT:CC**	**Toxic deaths HDT:CC**	**Comments**
Dopfer *et al*, 1991[13] (full paper)	–	PC	HDT + AIBMT [mainly ETOP/ CTX,TBI]	–	331	51	280						Patients received transplants at the discretion of the clinician and the parents. Results are given for all BMT group vs. two CC cohorts (early and late relapsers).
Comparison 1: early relapsers				–	–	51	165	–	–	65:32 2 years 52:22 4 years	NYR:11	–	Early relapse = patients that relapse on or within 6 months of completing initial maintenance chemotherapy.
Comparison 2: late relapsers				–	–	51	115	–	–	65:75 2 years 52:51 4 years	NYR:56.5	–	Late relapse = patients who relapse > 6 months after completion of maintenance chemotherapy.
Wheeler *et al*, 1996[28] (abstract)	–1993	PC	HDT + AIBMT	CC	170	–	–	11% reduction in the proportion dying	–	–	–	–	Very little detail given. Patients electively received an allogeneic transplant. Analysis was done on the basis of having the results of tissue typing available (i.e. donor vs. no donor). Some patients without a donor received autologous BMT; there is no indication of how many were included in this analysis.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 8 *On-going RCTs and RCTs not yet reported in paediatric ALL*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
CCG-1941†	Open	Childhood ALL Early first relapse	Induction [ETOP, IFOS/DMS, VCR, ASP, MTX/CF, MTX, CYT] HDT + ABMT/PBPCT/AIBMT (related or unrelated) [ETOP, TBI]	Induction [ETOP, IFOS/DMS, VCR, ASP, MTX/CF, MTX, CYT] Intensification [DMS, VCR, MTX/CF, TG, CYT, ETOP, ASP, IFOS/IDA, MTX, CYT] Maintenance [VCR, MTX, TG, CYT]	296
MRC-LEUK-UKALL-R2 EU-95039†	Open	Childhood ALL First relapse	Induction [DMS, VCR, EPI, ASP, MTX] Consolidation [3 cycles including VCR, ETOP, CYT, DMS, EPI, ASP, TG, CYT] HDT + AIBMT (matched/unmatched) [CTX, TBI]	Induction [DMS, VCR, EPI, ASP, MTX] Consolidation [3 cycles including VCR, ETOP, CYT, DMS, EPI, ASP, TG, CYT] Intensification [MTX, MP, CF] Maintenance [MTX, VCR, PRED, MP alternating with TG, ETOP, CYT, CTX, MTX]	200
MRC-LEUK-UKALL-R1-CH EU-92023†	Closed 01/04/95 (closed prematurely due to poor recruitment)	Childhood ALL First relapse	Induction [DMS, VCR, ASP, EPI, CYT, MTX] HDT + ABMT/AIMBT [CTX, TBI]	Induction [DMS, VCR, ASP, EPI, CYT, MTX] Intensification [3 cycles including ETOP, CYT, MTX, DMS, ASP, EPI, VCR, TG, CTX] Consolidation [MTX, CF, MP, CYT] Continuation [PRED, VCR, MTX, MP alternating with TG, ETOP, CYT, CTX, MTX]	255
Maximum planned accrual ...					**751**

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*
Shaded boxes indicate open UK-based and European Organization for Research and Treatment of Cancer (EORTC) trials.

Chapter 5

Review: adult acute lymphoblastic leukaemia

Introduction

The relative incidence of adult ALL – about 15–20% of acute adult leukaemias – is lower than that of paediatric ALL and its prognosis much worse. At presentation around 80–85% of patients achieve complete responses,[29] but long-term survival is only in the order of 20–30%.[30] This is, however, thought to be a reflection of the biology of the two diseases rather than of the treatment strategy used, because conventional therapy for adult ALL has been influenced by the success of the approach in treating children.

As with paediatric ALL, CC consists of intensive induction and consolidation phases, which are delivered in hospital and are often associated with a high morbidity and mortality, followed by maintenance therapy which is given on an outpatient basis over a 2-year period. Because of the relatively poor success of this conventional therapy and the length of the treatment, HDT with either allogeneic or autologous transplantation has been tested as an alternative in the consolidation of first remission, with the aim of increasing survival rates and decreasing treatment time.

At relapse, conventional treatment is intensive, not particularly effective and associated with considerable morbidity, mortality and expense. Therefore, there is a possibility that HDT with allogeneic support may also have a role in improving survival in second or third complete response, although the number of patients that attain such responses is very low.

Methods

The methods set out in chapter 2 were used. Three RCTs and six CCTs were identified. Data from other comparative studies were tabulated to provide supplementary qualitative information.

Results

Three RCTs and six CCTs were identified, all of which investigated the use of HDT/PCT in the consolidation of first remission (*Tables 9* and *10*).

One CCT compared the outcome for patients who had a donor with that for patients without a donor who were then randomised to either autologous transplantation or CC (results of this randomised portion of the trial are in *Table 9*).

RCTs comparing HDT/autologous transplantation with conventional therapy

Three RCTs[30–32] which randomised 213 patients to autologous BMT or CC were identified (*Table 9*). Each randomised adult patients in complete remission following induction therapy. Two trials[30,31] were conducted by the same group with the earlier trial[31] reported as the feasibility study for the second.[30] All trials were reported as full papers, although for one trial[30] some information was taken from a meeting abstract.[33] Patients were randomised between 1985 and 1991. No paper presented a survival curve, and only one[32] presented a PFS curve.

Survival

Neither of the papers[30,31] that provided information on survival found evidence of a difference between treatments. Because of the information available it was only possible to calculate an OR for one trial[30] at 5 years and therefore no summation of data could be performed.

PFS

No evidence of a difference in PFS between treatments was reported for any of the trials. A 2-year OR could be calculated for only one trial[32] and therefore no summation of data could be performed.

CCTs comparing HDT/allogeneic transplantation with conventional therapy

Six CCTs were identified which compared HDT/allogeneic BMT with conventional therapy in patients achieving a complete remission following induction therapy (*Table 10*). Five[34–38] compared HDT/allogeneic BMT with CC, and the sixth[30] compared HDT/allogeneic BMT with HDT/autologous BMT or CC. In total, 719 adult patients were entered into these trials from 1982 to 1991. It is believed that two publications[37,38] reported on the same trial despite discrepancies between the publications. The earlier abstract reported

on more patients, but the full paper[37] presented more complete information and has therefore been commented on and used in the combined analysis in this review.

The reporting of results was generally poor. Only two[30,34] out of five papers reported on survival. Both presented survival curves. All but one[34] of the reports presented some information on PFS and three[35–37] presented a PFS curve.

Survival

Of the two papers that reported survival, one[30] reported no evidence of a difference between HDT/allogeneic transplantation and CC. No statistical comment was made on the results of the second, small CCT.[34] However, the calculated OR at 2 years of 0.81 (99% CI 0.50–1.30) suggests no evidence of a difference between the two treatments modalities. No summation of data was performed owing to the differing control arms in these trials.

PFS

Two[30,35] publications reported no evidence of a difference between the two treatment arms. In a third trial,[36] HDT/PCT was compared with three chemotherapy regimens, two containing both consolidation and maintenance, and the third maintenance alone. The authors stated that there was no significant difference between HDT/PCT and the two CC regimens containing consolidation chemotherapy, but make no comment on the arm containing maintenance therapy alone. Using the total number of patients and events in all of the chemotherapy arms, the calculated 2-year OR of 0.39 (99% CI 0.15–1.04) favours HDT/PCT.

Mrsic and colleagues[37] reported a highly significant result in favour of HDT/PCT, but it is unclear with which chemotherapy regimen the HDT/PCT was compared; calculated ORs using the results of both control arms at 2 and 3 years are 0.39 (99% CI 0.12–1.24) and 0.26 (99% CI 0.08–0.87), respectively.

The combined 2-year OR of 0.38 (95% CI 0.22–0.65; *Table 11*) for trials comparing allogeneic transplantation with CC indicates an absolute survival benefit of approximately 23% (95% CI 11–35%) in favour of HDT/PCT (*Table 11*). As stated above, one paper[36] reported data on three chemotherapy regimens compared with a common HDT/PCT arm. The authors conclude that the maintenance-only arm performed significantly worse than both arms which contained consolidation and maintenance therapy. Performing a sensitivity analysis on the pooled 2-year OR, but including only the data from the two maintenance and consolidation arms of this trial, gives a combined OR for all trials of 0.45 (95% CI 0.26–0.79) which suggests an absolute survival advantage of 20% (95% CI 7–31%) also in favour of HDT/PCT.

Combining the calculated 3- and 4-year ORs (*Table 12*) from two trials[35,37] gave an overall OR of 0.23 (95% CI 0.10–0.51) which suggests an absolute survival benefit of approximately 35% (95% CI 15–51%) in favour of HDT/PCT.

Cohort studies comparing HDT/allogeneic transplantation with conventional therapy

Cohort studies comparing HDT/allogeneic transplantation with conventional therapy are presented in *Tables 13* and *14*. As previously discussed (chapter 3), it is usual for trials which randomised between autologous BMT and CC also to compare allogeneic transplantation with CC. This latter comparison does not constitute a true CCT and any such published results are tabulated in the cohort studies (*Table 14*).

Discussion

The RCTs and CCTs identified were generally relatively small and inconsistently reported. Many trials only reported on PFS.

HDT with autologous transplantation

Three RCTs have compared the use of HDT/autologous transplantation with CC in the consolidation of first remission in adult ALL; no evidence of a benefit for HDT/PCT was reported for any of these studies. Each of these trials was small and able to detect reliably only large differences in efficacy.

HDT with allogeneic transplantation

HDT with allogeneic transplantation, for consolidation of first remission, has been compared with conventional therapy in a number of controlled, but non-randomised, comparisons. Results for survival were reported for only two trials and in neither study was there any evidence of a difference between the treatments. Both trials were relatively small and therefore only large differences in treatment effect could have been detected. In addition, the protocol for one trial[34] was altered part way through so that patients without a suitable donor, deemed to be at high risk, were offered autologous transplantation. This change in protocol may have biased the results. The combined results suggest

that there may be some improvement in PFS, but this calculation does not include information from all trials and therefore is not a reliable summary of all trial data.

At present it is not possible to determine whether HDT with autologous or allogeneic transplantation offers any benefit over CC in the consolidation of first remission in adult ALL. Given the poor prognosis of adult ALL, the completion of more prospective trials is necessary to determine whether the benefits suggested by retrospective cohort studies are substantiated by the results of more reliable RCTs or CCTs. Participation in the on-going trials for both allogeneic and autologous transplantation (*Table 15*) should be encouraged.

TABLE 9 *RCTs comparing HDT/autologous PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Fiere *et al*, 1990[31] (full paper)	1985–86	C (2 cycles) HDT + ABMT (purged)	C (2 cycles) M	67	35	32	54:47 2.5 years	–	NS	0.75 (0.29–1.93) 2.5 years	–	–	NS	–	–	Crude survival is calculated from the number of reported events. Preliminary feasibility study prior to study below.[30,33] Poorly reported study. Transplants were purged. Authors state there are too few patients to come to any firm conclusions.
Sebban *et al*, 1994[30] (full paper) Fiere *et al*, 1994[33] (abstract)	1986–91	C (2 cycles) HDT + ABMT (purged) [CTX (120), TBI (12 Gy)]	C (2 cycles)	117	58	59	41:31 5 years	31:27	$p < 0.05$ in abstract $p = 0.7$ in paper[a]	0.68 (0.25–1.81) 5 years	–	19:13	$p = 0.6$	–	< 4 in total for both arms	Data taken from two references. Patients formed a large portion of the control patients in the study reported at the end of *Table 10*.[30,33] [a] Discrepancy in the quoted p values for survival. It is possible that the value from the abstract refers to a median survival, and that from the paper is for the LRT. Authors conclude that ABMT is not indicated for standard-risk patients, but is for high-risk patients.
Bernasconi *et al*, 1992[32] (full paper)	1987–90	EI HDT + ABMT	EI 2nd I	29	14	15	–	–	–	–	44:35 2 years	24:18	NS	0.68 (0.10–4.70) 2 years	–	Authors comment that there is a mixture of high- and low-risk patients and suggest that HDT needs evaluating in studies with better case selection.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*
Superscript letters cross-reference to comments column.
NS = not significant; LRT = log rank test; I = intensification.

TABLE 10 *CCTs comparing HDT/allogeneic PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Proctor *et al*, 1988[34] (full paper)	1982–86	I + C HDT + AlBMT [CTX (120), TBI (12 Gy)]	I + C M	29	–	8	21	63:49 2 years	33:18	–	0.81 (0.50–1.30) 2 years	–	–	–	–	3:–	After 1983 high-risk patients were offered autologous BMT.
Forman & Blume, 1991[35] (full paper)	1982–87	–	–	24	–	8	16	–	–	–	–	75:44 2 years 75:30 4 years	NYR:15	$p = 0.086$	0.30 (0.06–1.5) 2 years 0.15 (0.03–0.83) 4 years	–	Controls formed part of a multi-institutional trial of induction therapy. Authors suggest the need for larger trials.
Fiere *et al*, 1987[36] (full paper)	1983–85																CC was randomised to M ± C. Results for CC are given according to randomisation.
Comparison 1		–	C + M	–	–	38	38	–	–	–	–	72:53 2 years	NYR:29	NS	0.4 (0.14–1.55) 2 years	–	PFS was significantly ($p < 0.005$) longer in patients receiving C + M compared with M alone.
Comparison 2		–	C + M	–	–	38	32	–	–	–	–	72:64 2 years	NYR:NYR	NS	0.68 (0.18–2.52) 2 years	–	Authors state that BMT does not significantly increase PFS when compared with intensive consolidation chemotherapy.
Comparison 3		–	M	–	–	38	29	–	–	–	–	72:23 2 years	NYR:15	–	0.16 (0.04–0.56) 2 years	–	Many patients were omitted from the analysis. The number of patients included/omitted does not add up to total number of patients.
Overall results		–	–	169	31	38	99	–	–	–	–	–	–	–	0.39 (0.15–1.04) 2 years	–	Patients aged ≥ 40 years were ineligible for transplantation. From the text it is unclear whether such patients were included in the survival curves. The statistics quoted, however, are comparing the population aged < 40 years.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

Superscript letters cross-reference to comments column.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 10 contd *CCTs comparing HDT/allogeneic PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	PFS % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Mrsic *et al*, 1993[37] (full paper)	1983–91																One HDT cohort was compared with two CC regimens. Results for CC are reported according to regimen received.
Comparison 1		HDT + AIBMT [CTX + BU/TBI]	C + M	72	–	28	44	–:–	–:–	–	–	61:31 2 years	NYR: 12–15 months	$p < 0.001$[b]	0.31 (0.09–1.09) 2 years	–	Survival curves were not true actuarial survival curves. [b] It is not clear to which chemotherapy regimen this value refers.
												52:20 3 years			0.23 (0.06–0.85) 3 years		
Comparison 2		HDT + AIBMT [CTX + BU/TBI]	C + M	56	–	28	28	–	–	–	–	61:45 2 years	NYR: 12–15 months	$p < 0.001$[b]	0.57 (0.14–2.23) 2 years	–	
												52:30 3 years			0.36 (0.36–1.45) 3 years		
Overall results				100	–	28	72	–	–	–	–	–	–	–	0.39 (0.12–1.24) 2 years	13:0	OR calculated using the total number of patients/events in both chemotherapy regimens.
															0.26 (0.08–0.87) 3 years		
Mrsic *et al*, 1992[38] (abstract)	1983–91	HDT + AIBMT	–	140	–	55	85	–	–	–	–	54:15 3 years	–	–	0.16 (0.06–0.42) 3 years	–	Very little detail. This trial has the same patient entry dates as Mrsic *et al*, 1993,[37] and was run by the same hospital. It is assumed to be the same trial despite the discrepancy in patient numbers.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*
Superscript letters cross-reference to comments column.
The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 10 contd *CCTs comparing HDT/allogeneic PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Comparison of donor vs. no-donor (no-donor patients treated with both HDT/ABMT and CC)																	
Sebban *et al*, 1994[30] and Fiere *et al*, 1994[33] (full paper/ abstract)	1986–91	HDT + AIBMT [CTX, TBI]	C (2 cycles) or HDT + ABMT	257	0	116	141	60:56 2 years 52:41 4 years	51:30	$p = 0.08$[c]	0.84 (0.44–1.61) 2 years 0.65 (0.34–1.25) 4 years	45:31 5 years	24:22	$p = 0.1$[c]	0.54 (0.28–1.06) 5 years	18:4	[c] Analysis was for patients who underwent allogeneic BMT vs. all others, some of whom were randomised to autologous BMT vs. CC (see *Table 9*). Subset analysis performed which indicates that the high-risk patients perform significantly better with allogeneic BMT. Only tissue typed patients were included in this analysis.

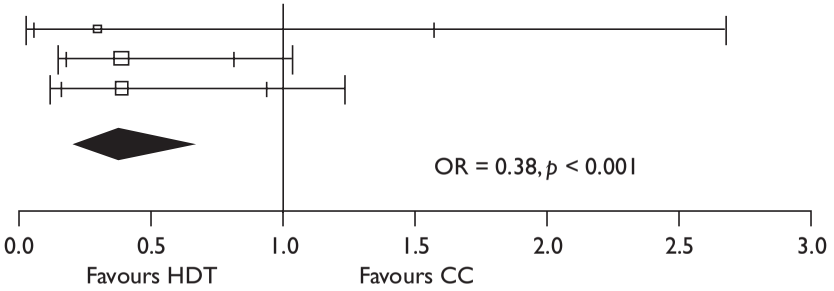
* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

Superscript letters cross-reference to comments column.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 11 *CCTs comparing HDT/allogeneic transplantation with CC in the consolidation of first remission in adult ALL: 2-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Forman & Blume, 1991[35]	2/8	9/16	–1.67	1.38	
Fiere *et al*, 1987[33]	11/38	52/99	–6.47	6.87	
Mrsic *et al*, 1993[37]	11/28	45/72	–4.68	5.02	
Total...	24/74	106/187	–12.8	13.27	

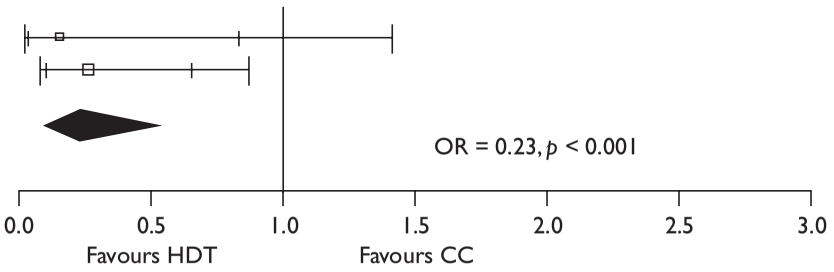


OR = 0.38 (95% CI 0.22–0.65) $\chi^2_{(1)} = 11.20, p < 0.001$ Het$\chi^2_{(2)} = 0.09, p = 0.96$

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 12 *CCTs comparing HDT/allogeneic transplantation with CC in the consolidation of first remission in adult ALL: 3- and 4-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Forman & Blume, 1991[35]	2/8	11/15	–2.52	1.34	
Mrsic *et al*, 1993[37]	13/28	55/72	–6.04	4.43	
Total...	15/36	66/87	–8.56	5.77	



OR = 0.23 (95% CI 0.10–0.51) $\chi^2_{(1)} = 12.70, p < 0.001$ Het$\chi^2_{(1)} = 0.28, p = 0.60$

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 13 *Cohort studies comparing HDT/autologous PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Proctor *et al*, 1988[34] (full paper)	1982–86	PC	HDT + ABMT [LPAM (3), TBI (10.5 Gy)]	–	31	10	21	82:49 2 years	NYR:18	–	–	0:–	After 1983 patients with a poor prognosis and no donor were offered an autologous transplant. There is no indication of the number of patients with a poor prognosis in the other control group.
Nemet *et al*, 1995[40] (abstract)	1988–94	PC	HDT + ABMT [CTX (120), TBI (12 Gy)]	C + M	37	18	19	–	–	–	–	–	Results are given as leukaemia-free survival: 22% for CC at 42 months and 48% for HDT at 71 months. Authors state that ABMT seems superior to CC in terms of leukaemia-free survival.
Proctor *et al*, 1994[39] (abstract)		PC	–	–									The study looked at two age groups, adolescents and adults. The overlap in age is as written in the abstract.
Comparison 1 (patients aged 25–60 years)	–	–	–	–	40	16	24	–	–	28:18 4 years	–	–	Population-based study.
Comparison 2 (patients aged 15–25 years)	–	–	–	–	31	18	13	–	–	56:36 3 years	–	–	CC contained more patients with 'favourable' features.
Diez-Martin *et al*, 1994[41] (abstract)	–	RCo	HDT + ABMT [CTX, RT]	–	38	11	27	–	–	57:– 2.4 years –:13 4 years	– –	6:– –	Very little information given. The authors concluded that ABMT may provide a significant proportion of long-term survivors. Five transplants were purged. The study included adults and children.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 14 *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Consolidation of first remission													
Zander *et al*, 1988[42] (full paper)	1980–85	PC	HDT + AlBMT [PIP (50), TBI (10.4 Gy)]	C + M	54	12	42	58:21[a] at time of analysis	–	–	–	7:–	[a] Survival values are crude survival not actuarial survival figures. Paper concentrates on the combined results of patients with ALL and AML compared with CC.
Zhang *et al*, 1995[43] (full paper)†	1980–87	RCo	HDT + AlBMT	–	718	234	484	–	–	34:32 9 years	–	53%:5%	High treatment-related mortality in the HDT arm. The toxic deaths presumably included much chronic GVHD. No details of the type of deaths were given. These data have been adjusted using a left-truncated Cox regression. HDT cohort taken from a bone-marrow registry.
Messerer *et al*, 1994[44] (full paper)†	1980–87	RCo	HDT + AlBMT [patients from BMTR]	–	453	182	271	–	–	48:61 2 years 43:44 4 years	–	–	Methodological paper investigating different methods for adjusting cohort data. Results are from the unadjusted survival data. HDT cohort taken from a bone-marrow registry.
Messerer *et al*, 1991[45] (full paper)	HDT: 1981–88 CC: 1980–86	RCo	HDT + AlBMT	–	76	38	38	–	–	46:51 2 years 41:31 4 years	–	–	Matched pair analysis. Survival curves adjusted to allow for short response durations in the chemotherapy arm and early remission in the transplantation arm. It is possible that patients included in this paper are also included in references 43 and 44.
Tamura *et al*, 1992[46] (full paper)	1982–89	RCo	HDT + AlBMT [CTX (120), TBI (10–12 Gy) or CTX (120), BU (20)]	–	30	12	18 2 years	92:73	NYR:40 2 years	84:49	76:26	1:0	Authors state that in their institution allogeneic BMT provided a favourable outcome compared with CC. Compared allogenic BMT with patients in remission for longer than 3 months.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

† *Results for patients treated at two German hospitals and patients from the International Bone Marrow Transplant Registry (IBMTR). It is very likely that many patients are included in the trials reported in references 43 and 44.*

Superscript letters cross-reference to comments column.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 14 contd *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Consolidation of first remission continued													
Fiere *et al*, 1990[31] (abstract)	1985–86	PC	HDT + AlBMT [CTX, TBI]	C (2 cycles)	71	39	32	–:47[b] at median follow-up at 2.5 years	–	–	–	2:0	[b] Crude survival data – no survival data given for HDT arm. Authors state that there was no difference between the two treatment groups.
Richards *et al*, 1996[47] (abstract)	1985–92	PC	HDT + AlBMT	–	–	–	–	11% fewer deaths in the donor group	–	–	–	–	Very few details given. Included both adults and children.
Bernasconi *et al*, 1992[32] (full paper)	1987–90	PC	HDT + AlBMT	–	31	16	15	–	–	46:35 2 years	–	–	Authors comment on the mixture of high- and low-risk patients, and suggest that HDT needs evaluating with better case selection. PFS curves cross.
Diez-Martin *et al*, 1994[41] (abstract)	–	RCo	C HDT + AlBMT [CTX, RT or BU, CTX]	–	39	12	27	–	–	33:– 5 years –:13 4 years	–	6:–	Very little information. Authors concluded that BMT may provide a significant proportion of long-term survivors. Mixture of adult and paediatric patients.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

Superscript letters cross-reference to comments column.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 14 contd *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of first remission in adult ALL*

Trial reference	Entry years	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Consolidation of first remission continued													
Proctor *et al*, 1994[39] (abstract)	–	PC	HDT + AIBMT	–									Split into two groups, adults and adolescents. The overlap in age group is as written in the abstract.
Comparison 1 (patients aged 25–60 years)	–	–	–	–	28	4	24	–	–	0:18 3 years	–	–	Population-based study.
Comparison 2 (patients aged 15–25 years)	–	–	–	–	24	11	13	–	–	50:36 3 years	–	–	
Consolidation of remission/relapse vs. first-line treatment													
Yoshida *et al*, 1984[48] (full paper)[c]	1978–83	RCo	HDT + AIBMT [CTX + TBI-based]	M	27	8	19	49:45 1 year	–	4:11.5	–	3:–	Very mixed HDT population, at different stages of disease. [c] In Japanese.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

Superscript letters cross-reference to comments column.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 15 *On-going RCTs and RCTs not yet reported in adult ALL*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
E-2993 EST-4491†	Open	ALL	Induction [2 cycles including DNR, VCR, PRED, ASP, MTX, CTX, CYT, MP, RT] Intensification [MTX, ASP, CF] HDT + ABMT/AlBMT [ETOP + TBI]	Induction [2 cycles including DNR, VCR, PRED, ASP, MTX, CTX, CYT, MP, RT] Intensification [MTX, ASP, CF] Consolidation [4 cycles including CYT, ETOP, VCR, DMS, DNR, CTX, CYT, TG] Maintenance [VCR, PRED, MP, MTX]	750
EORTC-06951†	Open	ALL	Induction [DNR, CTX, VCR, PRED, MTX or DNM, CTX,VCR, DMS] Intensification [CYT-DHAD, MTX or MTX, ASP] HDT + ABMT/AlBMT [CTX + TBI, MTX] Maintenance [VCR, ADR, DMS, MTX or VCR, ADR, PRD, MTX, MP, MTX or MP/MTX]	Induction [DNR, CTX, VCR, PRED, MTX or DNM, CTX, VCR, DMS] Intensification [CYT-DHAD, MTX or MTX, ASP] Consolidation [CTX, CYT, MP, MTX alternating with MTX, ASP, MP, MTX] Maintenance [VCR, ADR, DMS, MTX or VCR, ADR, PRD, MTX, MP, MTX]	392

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*
Shaded boxes indicate open EORTC trials.

continued

TABLE 15 contd *On-going RCTs and RCTs not yet reported in adult ALL*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
EORTC-06891†	Open	High-risk adult ALL	HDT + ABMT	Maintenance for 2.5 years	?
EORTC-06861†	Closed 04/09/96	ALL	Induction [DNM, CTX, PRED, VCR] Consolidation [ASP, VCR, PRED, CTX, CYT] HDT + ABMT/AIBMT [CTX,TBI] CNS prophylaxis/CNS therapy	Induction [DNM, CTX, PRED, VCR] Consolidation [ASP, VCR, PRED, CTX, CYT] Maintenance [PRED, VCR, ADR, BCNU, CTX, 6-MP, MTX, ACT-D] 6-MP, MTX, VCR, PRED, CNS prophylaxis/ CNS therapy	295
Maximum planned accrual ...					**>1437**

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*

Chapter 6

Review: paediatric acute myeloid leukaemia

Introduction

AML occurs less frequently in children than in adults and accounts for about 15–20% of the childhood leukaemias.[49] Unlike ALL, paediatric AML treated with CC carries a poor prognosis. Around 75–85% of children achieve a complete remission following initial chemotherapy[50] and the long-term survival is approximately 30–40%.[49] Outcome for those patients who relapse is much poorer with long-term survival about 5%.[51] Although similar in many respects to adult AML, there are genetic differences between these entities which suggest a reason for the poorer outcome in adult cases. For this reason adult and paediatric cases have not been analysed together.

Conventional treatment involves intensive chemotherapy, given as an in-patient, which is associated with significant mortality and morbidity. The long-term side-effects of treatment are likely to be particularly problematic in paediatric cases because of the effect on the developing child. However, children do appear to tolerate chemotherapy better than adults. Standard chemotherapy generally continues for 4–6 months, but unlike in ALL maintenance therapy is not used.

The efficacy of the HDT/PCT approach in the consolidation of first remission, particularly with autologous support, has been suggested in a number of cohort studies which has led to a number of RCTs being conducted. The activity of HDT with allogeneic support has also been demonstrated for the consolidation of first remission, but conducting properly randomised comparisons has proved difficult and trials have used quasi-random methods of allocating treatment according to donor availability as discussed in chapter 3.

Shortly after we undertook our systematic review we became aware that a more reliable meta-analysis based on individual patient data to investigate the role of HDT/autologous BMT as consolidation of first remission had been completed by the AML Collaborative Group (Clarke M, Clinical Trials Services Unit, Oxford: personal communication, 1997). However the results of the AML Collaborative Group project have not yet been published and it was decided to include the current results in our report as an interim measure. The results presented here are undoubtedly less reliable than those of the AML Collaborative Group (see appendix 6) and should therefore be replaced by the Collaborative Group's results when they become publicly available.

Methods

The methods set out in chapter 2 were used. Four RCTs and five CCTs were identified. Because of the amount of data available from RCTs and CCTs it was decided not to search for the results of cohort studies.

Results

Four RCTs were identified (*Table 16*) which randomised 712 children to autologous BMT or conventional therapy for the consolidation of first remission. Five CCTs (*Table 17*) were found which included more than 1000 patients receiving either an allogeneic transplantation or conventional therapy in the consolidation of first remission.

RCTs comparing HDT/autologous transplantation with conventional therapy

Four RCTs were identified which compared HDT/autologous transplantation with conventional therapy (*Table 16*). Three of the studies[52–54] compared HDT/PCT with CC, and the fourth[55] compared HDT/PCT with 'no further therapy'. A total of 712 patients were randomised across all trials between 1987 and 1995.

Of the reports on RCTs that were identified, two[52,53] were full papers, and two[54,55] were abstracts. Three publications[53–55] report survival data and one[53] presented a survival curve. All reports give PFS data, with PFS curves appearing in both full papers.[52,53]

Survival

Two publications[53,55] found no evidence of a difference between the two treatments for survival, whereas the Children's Cancer Group trial[54] reported preliminary results that were

significantly better in the CC arm. Combining the calculated 3- and 4-year ORs for 2 trials[53,54] gave an overall OR of 1.43 (95% CI 1.02–2.01; *Table 18*) suggesting an absolute survival benefit of approximately 8% (95% CI 0–16%) in favour of CC.

PFS

Three publications[53–55] reported no evidence of a difference between HDT/PCT and CC for PFS and although no statistical comment is made on the results of the fourth trial,[52] the calculated ORs at 2 and 4 years also gave no evidence of a difference between the two treatments. The pooled ORs were 1.14 (95% CI 0.72–1.81) at 2 years and 1.22 (95% CI 0.88–1.69) at 3 and 4 years (*Tables 19* and *20*) – at both time-points in favour of CC.

CCTs comparing HDT/allogeneic transplantation with conventional therapy

Five publications that reported the results of CCTs which compared HDT/allogeneic transplantation with conventional therapy were identified (*Table 17*). Four compared HDT/allogeneic transplantation with CC, and the fifth compared patients undergoing HDT/allogeneic transplantation with patients receiving HDT/autologous transplantation or 'no further therapy'. Patients were registered between 1979 and 1994.

Of the trials identified, four[56–59] were published as full papers, and one[55] was an abstract. Three publications[55,56,58] reported survival data, but only one paper[56] presented a survival curve. All papers reported PFS data, and all full papers presented PFS curves.

Survival

None of the publications[55,56,58] that reported survival data found any evidence of a difference between the two treatment modalities. The combined OR at 4 and 5 years is 0.69 (95% CI 0.50–0.96) suggesting an absolute survival difference of approximately 9% (95% CI 1–17%) in favour of HDT/PCT (*Table 21*).

PFS

Four publications[55–58] reported no significant difference between HDT/PCT and CC, whereas the fifth[59] found a conventionally significant benefit for HDT/PCT. The combined ORs are 0.63 (95% CI 0.48–0.84) at 2 years (*Table 22*) and 0.54 (95% CI 0.42–0.75) at 4 years (*Table 23*). This suggests an absolute survival benefit of approximately 11% (95% CI 4–17%) at 2 years and 15% (95% CI 8–21%) at 4 years, both in favour of HDT with allogeneic transplantation.

Cohort studies comparing HDT/allogeneic transplantation with conventional therapy

As previously discussed (chapter 3) it is usual for trials which randomised between autologous BMT and CC also to compare allogeneic transplantation and CC. This latter comparison is essentially a cohort study and although no literature search was carried out to identify other cohort studies, the results of these comparisons are tabulated for completeness (*Table 24*).

Discussion

HDT with autologous transplantation

Although HDT including autologous support has been compared with conventional therapy in a number of RCTs, the results of these trials are currently immature and should be interpreted cautiously. The results of four trials including a total of 712 children have been published: three compared HDT/autologous transplantation with CC and the fourth compared HDT/autologous transplantation with 'no further therapy'. None of these studies offers convincing evidence of the superiority of one approach over the other, and those trials which compared HDT/PCT with CC all tend to favour conventional therapy. Consequently, at present, it is not possible to draw firm conclusions or recommend one treatment approach over the other.

HDT with allogeneic transplantation

HDT with allogeneic transplantation has been compared with conventional therapy in a number of controlled but non-randomised comparisons. The results from the four trials which compared HDT/allogeneic transplantation with CC only,[56–59] which included a total of 1021 children, suggest a benefit in favour of HDT/PCT. However, the reporting of these trials was poor, particularly with respect to survival. Only two of these publications[56,58] presented survival data which when combined gave a conventionally significant benefit in favour of HDT with allogeneic transplantation at 4 years. Similarly, the combined results, from four trials,[56–59] for PFS at both 2 and 4 years suggest conventionally significant benefits for HDT with allogeneic transplantation. The results of the MRC trial[55] comparing HDT/allogeneic transplantation with HDT/autologous transplantation or 'no further therapy' are preliminary and at present there is no evidence of a difference between the two treatments. Although the results of the identified CCTs suggest some benefit for allogeneic transplantation, these results must be interpreted

with caution in view of the potential bias associated with non-randomised studies.

Further research is undoubtedly required to determine whether or not HDT with either autologous or allogeneic support is more effective than conventional treatment of first remission paediatric AML. Recruitment into currently on-going studies (*Table 25*) and the establishment of further prospective trials should be encouraged. It must also be noted that although treatment-related mortality is lower among children than in adults, the intensive treatments used may be associated with more long-term side-effects such as growth retardation and secondary malignancies; such trials must therefore ensure adequate long-term follow-up.

TABLE 16 *RCTs comparing HDT/autologous PCT with CC in the consolidation of first remission in paediatric AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Amadori *et al*, 1993[52] (full paper)	1987–90	C (1 cycle) HDT + ABMT [BAVC]	C (1 cycle) C (5 cycles) + M	72	0	35	37	–	–	–	–	26:34 2 years 21:27 4 years	10:11	–	1.55 (0.42–5.74) 2 years 1.47 (0.35–6.08) 4 years	1:3	Authors comment that the results of the BMT arm are worse than those of recent trials and suggest that the BAVC may not be optimal.
Ravindranath *et al*, 1996[53] (full paper)	1988–93	C (1 cycle) HDT + ABMT [BU (16), CTX (200]	C (1 cycle) C (6 cycles)	232	0	115	117	45:52 2 years 40:42 4 years	19:30	RR = 0.75 (0.53–1.06) in favour of CC[a] p = 0.1	1.32 (0.67–2.59) 2 years 1.08 (0.54–2.15) 4 years	39:40 2 years 38:35 4 years	10:14	RR = 0.81 (0.58–1.12) in favour of CC[a] p = 0.2	1.04 (0.52–2.08) 2 years 0.87 (0.43–1.76) 4 years	11:3	[a] RR favours CC (RR calculated with respect to CC). Authors comment on low overall survival in both study arms and suggest that the induction chemo-therapy may not have been optimal.
Woods *et al*, 1996[54] (abstract)	1989–95	HDT + ABMT (purged) [CYT + other drugs]	–	310	–	150	160	45:59 3 years	–	p = 0.03	1.75 (0.98–3.15) 3 years	40:50 3 years	–	p = 0.1	1.50 (0.83–2.69) 3 years	–	Transplant was purged. Authors conclude that CC should be used in preference to BMT.
Trial comparing HDT with NFT:																	
Stevens *et al*, 1995[55] (abstract)	1988–94	C (2 cycles) HDT + ABMT	C (2 cycles)	98	–	–	–	71:64 5 years	–	p = 0.7	–	68:48 5 years	–	p = 0.1	–	–	This trial included adult patients following the same protocol. An analysis of all patients is in *Table 26*. Authors conclude that to date there is no evidence of a benefit for autologous BMT. Updated 7-year results are in press.

* *See list of abbreviations of drug names on page ii. BAVC: BCNU (total dose 450 mg/m^2); AMSA (450 mg/m^2); ETOP (800 mg/m^2); CYT (900 mg/m^2).*

NFT = no further therapy; RR = relative risk.

Superscript letters cross-reference to comments column.

TABLE 17 *CCTs comparing HDT/allogeneic PCT with CC in the consolidation of first remission in paediatric AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	PFS % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Nesbit *et al*, 1994[56] (full paper)	1979–83	HDT + AlBMT [CTX (120), TBI (7.5–10 Gy)]	M[a]	341	0	89	252	55:49 2 years 51:38 4 years	69:21	$p = 0.25$	0.78 (0.41–1.47) 2 years 0.60 (0.31–1.14) 4 years	51:40 2 years 47:34 4 years	27:15	$p = 0.12$	0.65 (0.34–1.24) 2 years 0.57 (0.30–1.11) 4 years	–	[a] Randomised to either cyclic or continous. All patients with siblings were genetically typed. Unclear as to whether PFS curve is ITT. PFS curves cross. Authors concluded that patients eligible for an allogeneic BMT survive better than those not eligible for a transplant.
Dahl *et al*, 1990[57] (full paper)	1980–83	HDT + AlBMT [CTX (120), TBI (12 Gy)]	M	65	4	19	42	–	–	–	–	58:39 2 years 58:29 4 years	66:21	$p = 0.33$	0.45 (0.11–1.88) 2 years 0.29 (0.07–1.26) 4 years	5:2	Only typed patients included. BMT must have been performed within 16 weeks of typing. Authors comment that it would be difficult to identify a group of patients likely to benefit from HDT.
Wells *et al*, 1994[58] (full paper)	1986–89	HDT + AlBMT [CTX (120), TBI (10–12 Gy)]	C (3 cycles) Randomised to M or NFT	411	0	113	298	52:46 5 years	–	$p = 0.29$	– 0.78 (0.44–1.38) 5 years	53:46 2 years 47:38 4 years	30:17	$p = 0.27$	0.75 (0.43–1.33) 2 years 0.69 (0.39–1.23) 4 years	–:26	Only typed patients were included. Authors comment on high treatment-related mortality in the CC arm and the high percentage of patients who did not receive allocated treatment (27% in the HDT arm).

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

ITT = intention to treat.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 17 contd *CCTs comparing HDT/allogeneic PCT with CC in the consolidation of first remission in paediatric AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Michel *et al*, 1996[59] (full paper)	1988–93	C (0–3 cycles) HDT + AIBMT [CTX, BU or TBI (doses varied)]	C + M	204	–	53	151	–	–	–	–	73:55 2 years 68:48 4 years	NYR:44	$p = 0.02$	0.4 (1.01–0.20) 2 years 0.38 (0.14–1.04) 4 years	3:11	All patients were tissue typed. HDT group were significantly older. Two patients in the HDT arm had no sibling donor but were given marrow from a mis-matched parent. Authors conclude that allogeneic transplant is the treatment of choice.
Trial of donor vs. no donor:																	
Stevens *et al*, 1995[55] (abstract)	1988–94	C (1 cycle) HDT + AIBMT	C (2 cycles) HDT + ABMT or NFT	–	–	–	–	66:60 5 years	–	$p = 0.2$	–	61:52 5 years	–	$p = 0.5$	–	–	Authors comment that the survival benefit, if any, of allogeneic BMT is small and may not warrant the toxicity at least for low-risk patients. This trial is a portion of a larger trial which included adult patients following the same protocol. An analysis of all patients is presented in *Table* 27. Updated 7-year results are in press.

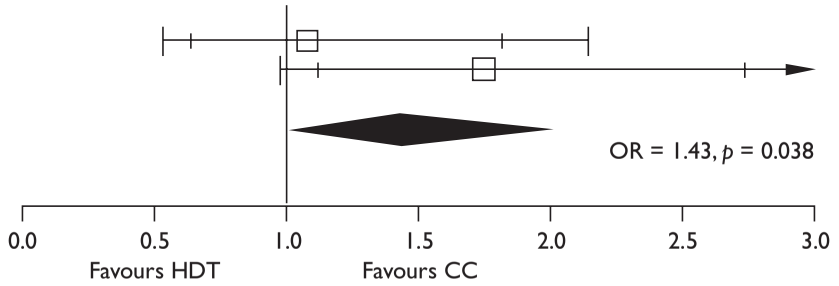
* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

ITT = intention to treat.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 18 *RCTs comparing HDT/autologous transplantation with CC for the consolidation of first remission in paediatric AML: 3- and 4-year survival*

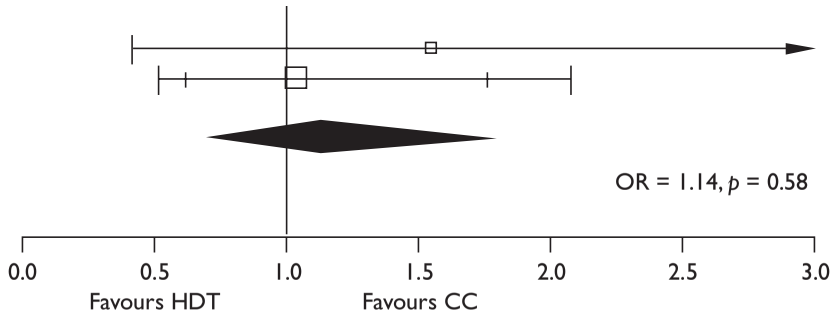
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Ravindranath *et al*, 1996[53]	69/115	68/117	1.09	14.08	
Woods *et al*, 1996[54]	83/150	66/160	10.90	19.39	
Total…	152/265	134/277	11.99	33.47	



OR = 1.43 (95% CI 1.02–2.01) $\chi^2_{(1)} = 4.95, p = 0.038$ Het$\chi^2_{(1)} = 1.92, p = 0.16$

TABLE 19 *RCTs comparing HDT/autologous transplantation with CC for the consolidation of first remission in paediatric AML: 2-year PFS*

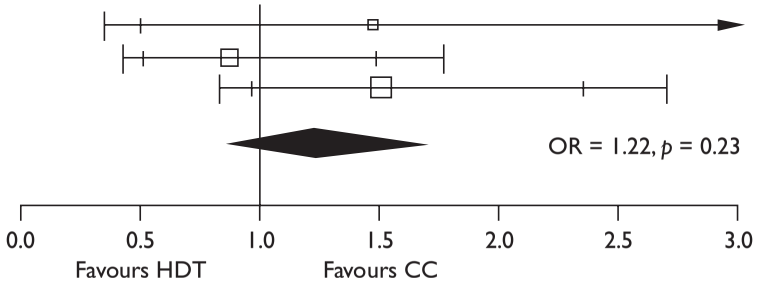
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Amadori *et al*, 1993[52]	26/35	24/37	1.69	3.87	
Ravindranath *et al*, 1991[53]	70/115	70/117	0.60	13.94	
Total…	96/150	94/154	2.30	17.81	



OR = 1.14 (95% CI 0.72–1.81) $\chi^2_{(1)} = 0.297, p = 0.58$ Het$\chi^2_{(1)} = 0.47, p = 0.49$

TABLE 20 *RCTs comparing HDT/autologous transplantation with CC for the consolidation of first remission in paediatric AML: 3- and 4-year PFS*

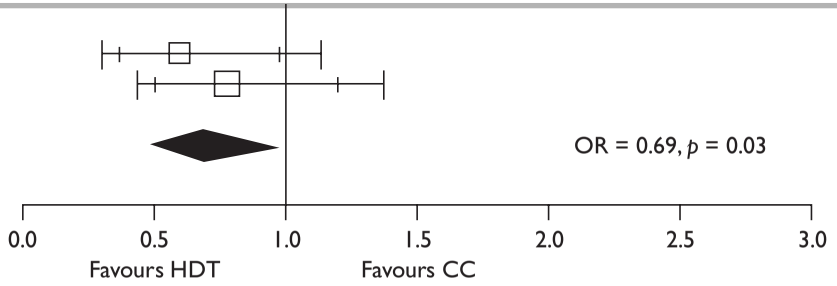
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Amadori *et al*, 1993[52]	28/35	27/37	1.26	3.29	
Ravindranath *et al*, 1996[53]	71/115	76/117	–1.87	13.52	
Woods *et al*, 1996[54]	90/150	80/160	7.74	19.24	
Total…	189/300	183/314	7.14	36.05	OR = 1.22, p = 0.23



OR = 1.22 (95% CI 0.88–1.69) $\chi^2_{(1)}$ = 1.41, p = 0.23 Het$\chi^2_{(2)}$ = 2.45, p = 0.29

TABLE 21 *CCTs comparing HDT/allogeneic transplantation with CC for the consolidation of first remission in paediatric AML: 4- and 5-year survival*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Nesbit *et al*, 1994[56]	44/89	156/252	–8.20	16.00	
Wells *et al*, 1994[58]	54/113	161/298	–5.11	20.49	
Total…	98/202	317/550	–13.30	36.49	OR = 0.69, p = 0.03

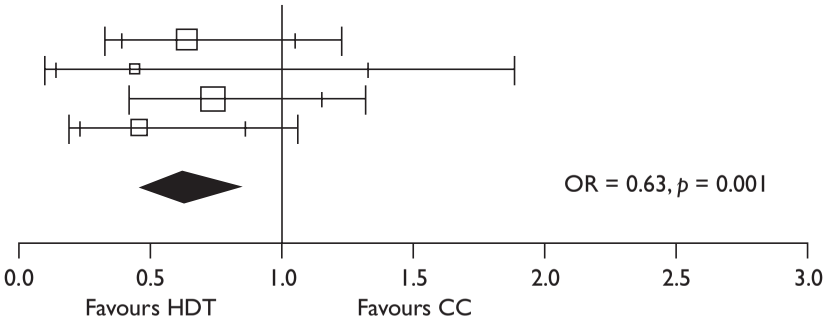


OR = 0.69 (95% CI 0.50–0.96) $\chi^2_{(1)}$ = 4.85, p = 0.03 Het$\chi^2_{(1)}$ = 0.62, p = 0.43

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 22 *CCTs comparing HDT/allogeneic transplantation with CC for the consolidation of first remission in paediatric AML: 2-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Nesbit *et al*, 1994[56]	44/89	151/252	–6.89	16.15	
Dahl *et al*, 1990[57]	8/19	26/42	–2.59	3.28	
Wells *et al*, 1994[58]	53/113	161/298	–5.84	20.50	
Michel *et al*, 1996[59]	14/53	68/151	–7.30	9.48	
Total…	119/274	406/743	–22.60	49.41	OR = 0.63, p = 0.001

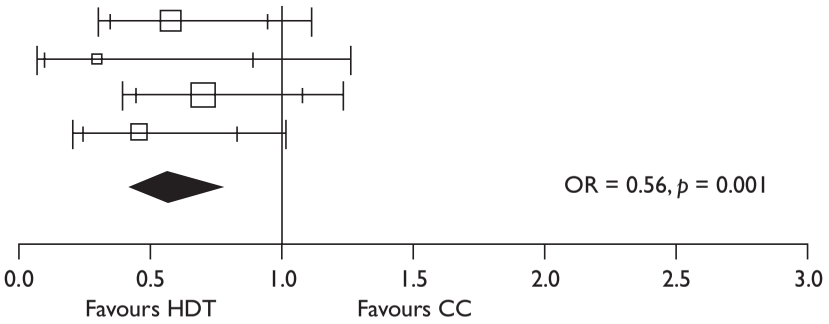


OR = 0.63 (95% CI 0.48–0.84) $\chi^2_{(1)}$ = 10.35, p = 0.001 Het$\chi^2_{(3)}$ = 1.92, p = 0.58

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 23 *CCTs comparing HDT/allogeneic transplantation with CC for the consolidation of first remission in paediatric AML: 4-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Nesbit *et al*, 1994[56]	47/89	166/252	–8.59	15.47	
Dahl *et al*, 1990[57]	8/19	30/42	–3.84	3.12	
Wells *et al*, 1993[58]	60/113	185/298	–7.36	19.77	
Michel *et al*, 1996[59]	17/53	79/151	–7.94	9.82	
Total…	132/274	460/743	–27.70	48.19	OR = 0.56, p = 0.001



OR = 0.56 (95% CI 0.42–0.75) $\chi^2_{(1)}$ = 15.96, p < 0.001 Het$\chi^2_{(3)}$ = 2.69, p = 0.44

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 24 *Cohort studies comparing HDT/allogeneic PCT with CC in the consolidation of first remission in paediatric AML*

		Treatment regimen*		No. of patients				Survival		PFS			
Trial reference	**Entry years**	**HDT (total dose, mg/m^2)**	**CC**	**Total**	**Ex-cluded**	**BMT**	**CC**	**% HDT:CC**	**Median (months) HDT:CC**	**% HDT:CC**	**Median (months) HDT:CC**	**Toxic deaths HDT:CC**	**Comments**
Amadori *et al*, 1993[52] (full paper)	1987–90	C (1 cycle) HDT + AIBMT [CTX (120), TBI (12 Gy)]	C (1 cycle) C (6 cycles)	61	0	24	37	–	–	66:34 2 years 51:27 4 years	NYR:11	0:3	Authors conclude that allogeneic BMT is the most effective treatment in terms of PFS, but make no comment on survival.
Ravindranath *et al*, 1996[53] (full paper)	1988–93	C (1 cycle) HDT + AIBMT [recommended BU + CTX]	C (1 cycle) C (6 cycles)	206	–	89	117	68:52 2 years	NYR:30	61:42 2 years 52:35 4 years	NYR:14	–:3	Authors comment that this comparison did not form a major part of this study.
Woods *et al*, 1996[54] (abstract)	1989–95	HDT + AIBMT [BU, CTX]	–	300	–	140	160	76:59 3 years	–	70:50 4 years	–	–	Authors comment that patients with a sibling donor should receive an allogeneic transplant.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 25 *On-going RCTs and RCTs not yet reported in paediatric AML*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
EORTC-58921†	Open	Childhood AML or myelodysplastic syndrome	Induction [CYT, IDA, ETOP, CYT or CYT, ETOP, MTOX] HDT + AIBMT [CTX, BU or CTX,TBI]	Induction [CYT, IDA, ETOP, CYT or CYT, ETOP, MTOX] Intensification [3 cycles including MTX/IDA, DNR, CYT, TG, ETOP, DMS, RT] Maintenance [CYT, TG]	310
POG-9421†	Open	Childhood AML	Induction [DNR, CYT, TG] HDT+ AIBMT [ETOP,TBI] MTX	Induction [DNR, CYT, TG] Consolidation [3 cycles including MTX, ETOP, CYT ± cyclosporine]	600
CCG-2961†	Open	Childhood AML	Induction [IDA, DMS, CYT, TG, ETOP, DNR, ETOP, DNR] Consolidation [IDA, DMS, CYT, TG, ETOP, DNR, ETOP, DNR or FAMP, CYT, IDA] HDT + AIBMT [BU, CTX] MTX	Induction [IDA, DMS, CYT, TG, ETOP, DNR, ETOP, DNR] Consolidation [IDA, DMS, CYT, TG, ETOP, DNR, ETOP, DNR or FAMP, CYT, IDA] CYT, ASP or CYT, MTX	880

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*
Shaded boxes indicate open UK-based and EORTC trials.

continued

TABLE 25 contd *On-going RCTs and RCTs not yet reported in paediatric AML*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
MRC AML12	Open	AML	HDT + AIBMT	CC	1000‡
CCG-2891†	Closed	Childhood AML or myelodysplastic syndrome	DMS, DNR, CTX, TG, ETOP HDT + ABMT (purged)/AIBMT [BU, CTX] Single agent chemotherapy MTX	DMS, DNR, CTX, TG, ETOP Intensification [4 cycles including CYT, ASP, VCR, CTX, TG, DNR, CYT, TG, DMS, ETOP]	900
Maximum planned accrual …					**3660**

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*
‡ *It is probable that this total represents the total number of patients who enter the trial at presentation, and therefore the number randomised to HDT vs. CC will be much lower.*
Shaded boxes indicate open UK-based and EORTC trials.

Chapter 7

Review: adult acute myeloid leukaemia

Introduction

In adults, AML accounts for 80–85% of acute leukaemia cases.[49] Incidence increases with age and treatment results appear worse in older age groups both because of the difficulty in delivering treatment and the perceived biological differences in the disease process. Using conventional treatment about 70–80% of patients younger than 65 years enter first remission;[60] however, this is associated with a long-term survival rate of only approximately 15–25%.[49] Investigators have therefore evaluated the use of HDT with allogeneic or autologous transplantation in the consolidation of first remission, as a means of preventing relapse and improving survival.

At the time of relapse intensive chemotherapy is thought to be required to induce further remissions, and at this point the remission rates attained are much lower than at presentation. Prolonged remission is unlikely and HDT/PCT has been used in an attempt to increase the duration of second remission.

In the UK, a large proportion of AML patients aged 65 years or younger are entered into national MRC trials and this has ensured some degree of uniformity in the approach to treatment. CC is intensive, generally takes around 3–5 months to complete and is associated with longer periods of hospitalisation than is HDT with autologous support.

Shortly after we undertook our systematic review we became aware that a more reliable meta-analysis based on individual patient data to investigate the role of HDT/autologous BMT as consolidation of first remission had been completed by the AML Collaborative Group (Clarke M, Clinical Trials Services Unit, Oxford: personal communication, 1997). However the results of the AML Collaborative Group project have not yet been published and it was decided to include the current results in our report as an interim measure. The results presented here are undoubtedly less reliable than those of the AML Collaborative Group (see appendix 6) and should therefore be replaced by the former when they become publicly available.

Methods

The methods set out in chapter 2 were used.

First remission

Five RCTs were identified which investigated the use of HDT with autologous transplantation compared with conventional therapy in the consolidation of first remission. An additional trial[61] was identified which reports results of the comparison of HDT/PCT with CC for a mixture of randomised and non-randomised patients and although these data are presented in the table and ORs have been calculated, no comment is made on these results and the results have not been used in any data synthesis. Ten CCTs comparing HDT/PCT with CC were identified. Because of the amount of data available from RCTs and CCTs it was decided not to search for the results of cohort studies.

Second remission

No RCTs or CCTs were identified. Two retrospective cohort studies were found, although it is likely that some patients are included in both studies.

Results

First remission

Data from RCTs and CCTs comparing HDT/PCT with conventional therapy for the consolidation of first remission in adult AML are shown in *Tables 26* and *27*.

RCTs comparing HDT/autologous transplantation with conventional therapy

Five RCTs were identified which compared autologous transplantation with conventional therapy in first remission (*Table 26*). Four[62–65] compared HDT/PCT with CC. The fifth[66] compared HDT/PCT with 'no further therapy' and included some paediatric patients. A total of 928 individuals (including children) were randomised across all trials between 1984 and 1994.

Of the five publications identified, three[62–64] were full papers, and two were abstracts[65,66] (*Table 26*). Two publications[62,64] are from the same trial group, and although updates of the earlier trial[62] have

been reported, the results have been combined with the results of the later trial.[64] One of latest updates of trials from this group[67] also contains patients from a third trial which has not been reported separately. The most recent reference for each individual trial is tabulated.

Four publications[63–66] reported information on survival, but only the full paper[63] presented a survival curve. All but one publication[66] reported on PFS, but the data given for one trial[64] did not include deaths from all causes as events; a true PFS curve appeared in only one paper.[63]

Survival

None of the publications,[63–66] giving survival information reported any evidence of a difference between treatments. Pooling the calculated 4-year results gives a combined OR of 0.89 (95% CI 0.64–1.29) (*Table 28*) in favour of HDT/PCT.

PFS

Of the three publications that reported PFS,[62,63,65] no significant difference between treatments was reported in one trial[65] and a result of borderline significance in favour of HDT/PCT was reported for a second.[63] The third trial[62] reported no statistical information, but a calculated OR of 0.28 (95% CI 0.04–2.04) at 2.5 years showed no evidence of a difference between treatments. However, combined ORs for 2 and 4 years were 0.57 (95% CI 0.36–0.93) and 0.61 (95% CI 0.41–0.90), respectively (*Tables 29* and *30*), which suggests an absolute survival benefit of approximately 14% (95% CI 2–23%) at 2 years and 12% (95% CI 3–22%) at 4 years, both favouring HDT/PCT.

CCTs comparing HDT/allogeneic transplantation with conventional therapy

Eight full papers and three abstracts were identified (*Table 27*) which compared HDT/allogeneic transplantation with CC for the consolidation of first remission in adults (two trials[68,66] included both adult and paediatric patients). Ten trials compared the outcome for patients with a donor[60,68–76] (allocated allogeneic transplantation) with the outcome for patients without a donor allocated CC. One trial[66] randomised patients without a donor to autologous transplantation or 'no further therapy' but all patients without a donor were analysed in the no-donor arm, regardless of whether they were actually randomised. Across all trials over 900 patients were registered between 1977 and 1994.

Only three full papers[60,69,70] and one abstract[76] reported information on both survival and PFS. Four publications[66,71,73,74] reported only results for survival, all but one[73] of which presented a survival curve. Three publications[68,72,75] presented only PFS data, and two published PFS curves.[68,72]

Survival

Five publications[60,66,70,71,73] reported no evidence of a difference between allogeneic transplantation and conventional therapy. Two publications[69,74] made no statistical comment on their results but sufficient information was presented to calculate ORs, both of which favoured HDT/PCT (*Table 27*). In an abstract, Dinsmore and colleagues[76] reported only crude survival figures at the time of analysis, and it was not possible to calculate an OR.

Combined analysis at 2 and 4 years gave ORs of 0.87 (95% CI 0.56–1.35) and 0.31 (95% CI 0.21–0.45), respectively (*Tables 31* and *32*) which suggests an absolute survival benefit of approximately 26% (95% CI 19–32%) at 4 years. The calculated OR for the preliminary report from one study[74] is extreme and because of the limited information reported in the abstract, can only be included in the combined analysis at 4 years. It is very possible that this poorly reported trial is not a true CCT but simply a cohort study, but there is insufficient information to assess this properly. A sensitivity analysis omitting this trial gives a combined OR at 4 years of 0.82 (95% CI 0.50–1.32).

PFS

Five publications[60,68,70,72,75] report no evidence of a difference between the two therapies in terms of PFS. For one of these trials[75] allogeneic transplantation was compared with two chemotherapy regimens, neither of which was significantly different from the HDT/PCT arm. One publication[69] reports a significant difference in favour of HDT/PCT, but this trial had a very short follow-up. In an abstract Dinsmore and colleagues[76] make no statistical comment on the findings, and there is insufficient information to calculate an OR.

Hewlett and colleagues[72] present PFS data for patients who received transplants, patients with donors but who did not receive a transplant, and CC patients. The calculated OR used the total number of events in the combined groups of patients who had a potential donor. However, the paper does report a non-significant *p* value for the log rank test of donor versus no donor.

The combined ORs at 2 and 4 years are 0.49 (95% CI 0.31–0.66) and 0.47 (95% CI 0.29–0.77) respectively, which suggests an absolute survival benefit of approximately 16% (95% CI 10–26%) at 2 years and 18% (95% CI 7–29%) at 4 years in favour of

patients receiving allogeneic transplantation (*Tables 33* and *34*).

Cohort studies comparing HDT/allogeneic transplantation with conventional therapy

As previously discussed (chapter 3) it is usual for trials which randomised between autologous BMT and CC also to compare allogeneic transplantation and CC. This latter comparison is essentially a cohort study and although no literature search was carried out to identify other cohort studies, the results of these comparisons are tabulated for completeness (*Table 35*).

HDT/PCT in second remission

The results from two retrospective cohort comparing HDT/allogeneic transplantation with CC for the consolidation of second remission in AML summarised in *Table 36*.

Discussion

A total of four trials, including 553 adult patients with AML, which compared HDT/autologous support with CC have been published. There was no good evidence of a survival difference in any of these trials or in the combined results. There was however some suggestion that HDT/PCT might improve PFS, with all trials favouring HDT/PCT and the combined OR reaching conventional levels of significance. The trial reporting on the comparison of autologous transplantation and 'no further therapy' also found no evidence of a difference in survival at 5 years. Further research is undoubtedly needed to confirm whether HDT with autologous transplantation increases PFS and to determine whether such PFS benefit is translated to a survival benefit. There is currently one on-going trial (*Table 37*) in which participation should be encouraged.

HDT including allogeneic transplantation has been compared with CC in a number of controlled, but non-randomised, comparisons. Consequently, although encouraging, the results from ten trials including over 900 patients must be interpreted with caution. The reporting of these trials was incomplete, with just over half presenting survival data. Although the combined results appear to suggest a survival benefit of HDT/PCT at 4 years, this is driven largely by the results of the study by Labar and colleagues.[74] It was difficult to discern whether or not that study was a CCT or cohort study and the results are extreme. Without the results of the study by Labar and colleagues,[74] there is no clear evidence of a survival difference between the two treatment approaches. As for survival, there is some suggestion that HDT/PCT might offer an advantage over conventional therapy in terms of PFS, with the combined ORs at 2 and 4 years reaching conventional levels of significance. However, given the potential bias associated with non-randomised studies, such results must be interpreted cautiously and further research is required to confirm this observation. There is currently one on-going trial (*Table 37*) in which participation should be encouraged.

TABLE 26 *RCTs comparing HDT/autologous PCT with CC in the consolidation of first remission in adult AML*

		Treatment regimen*		No. of patients				Survival				PFS					
Trial reference	**Entry years**	**HDT (total dose, mg/m^2)**	**CC**	**Total**	**Ex-cluded**	**HDT**	**CC**	**% HDT:CC**	**Median (months) HDT:CC**	**Statistics in paper**	**Calculated OR (99% CI)**	**% HDT:CC**	**Median (months) HDT:CC**	**Statistics in paper**	**Calculated OR (99% CI)**	**Toxic deaths HDT:CC**	**Comments**
Reiffers *et al*, 1989[62] (full paper)	1984–86	C (1 cycle) HDT + ABMT (2 transplants) [L-PAM (140), between transplants CYT, ETOP]	C (1 cycle) C [4 cycles + cranial RT]	58	0	15	20	–	–	–	–	41:16 2.5 years	–	–	0.28 (0.04–2.04) 2.5 years	0:1	Two transplants given. PFS curve based on treatment received, ITT information is in the text and little information is presented. Updated information on the patients in this trial appears in many publications. However, the patients are combined with patients from two other trials. Authors make little comment regarding the chemotherapy vs. autologous comparison.
Zittoun *et al*, 1995[63] (full paper)	1986–93	C (1 cycle) HDT + ABMT [CTX (120), TBI]	C (1 cycle) C (1 cycle)	254	0	128	126	63:66 2 years 56:46 4 years	NYR:31	RR = 0.86 (95% CI 0.59–1.25) p = 0.43	1.22 (0.57–2.20) 2 years 0.67 (0.53–1.27) 4 years	50:38 2 years 48:30 4 years	24:18	RR = 0.73 (0.52–1.00) p = 0.05	0.62 (0.32–1.18) 2 years 0.49 (0.25–0.93) 4 years	9:12	12 patients in the HDT group did not complete treatment due to early relapse; five patients in the CC arm did not complete treatment. Authors note that 24 of the 36 patients who relapsed in the CC arm went on to receive BMT. Survival curves cross. Authors conclude that any benefit for HDT is limited to PFS.

* *See list of abbreviations of drug names on page ii.*
Superscript letters cross-reference to comments column.

continued

TABLE 26 contd *RCTs comparing HDT/autologous PCT with CC in the consolidation of first remission in adult AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Reiffers *et al*, 1993[64] (full paper)	1987–90	C (1 cycle) HDT + ASCT [BU (16), L-PAM (140)]	C (1 cycle) C (5 cycles) M (2 years)	77	0	39	38	56:55 3 years	–	NS	0.96 (0.39–2.33) 3 years	56:55 2 years 48:40 4 years	37:25	NS	–	2:0	Mixture of BMT and PBPCT. Authors concluded that the best treatment for AML is still debatable. PFS does not include death from any cause.
Harousseau *et al*, 1996[65] (abstract)	1987–94	C (1 cycle) HDT + ABMT [BU (16), CTX (800)]	C (1 cycle) C (1 cycle)	164	0	86	78	48:57 4 years	–	NS	1.35 (0.60–3.00) 4 years	42:38 4 years	–	NS	0.87 (0.38–1.97) 4 years	–	Authors conclude that BMT and CC are similar.
Hubner *et al*, 1996[61a] (full paper)	1988–91	C (1 cycle) HDT + ABMT [BU (16), CTX (120)]	C (1 cycle) C (1 or 2 cycles)	18[b]	–	10[b]	8[b]	49:65 2 years 33:46 4 years	28:36	$p = 0.19$	–	27:41 2 years 18:36 4 years	11:16	0.15	–	0:2	[a] Trial includes both randomised and non-randomised patients. [b] Number of randomised patients. All patients: 56 in total (HTD, 12; CC, 44). Randomisation was halted due to the high.number of relapses on the HDT arm of the trial. It is inappropriate to calculate ORs because of the mixture of randomised and non-randomised patients included in the cohorts.
Trial comparing ABMT vs.NFT																	
Burnett *et al*, 1994[66] (abstract)	1988–94	C (2 cycles) HDT + ABMT	C (2 cycles) NFT	357	–	–	–	54:52 5 years	–	$p = 0.8$	–	–	–	–	–	11%:–	Includes adult and paediatric patients (analysis of paediatric patients alone is in *Table 55*).

* *See list of abbreviations of drug names on page ii.*
Superscript letters cross-reference to comments column.
ASCT = autologous stem cell transplant

TABLE 27 *CCTs comparing HDT/allogeneic PCT with conventional therapy in the consolidation of first remission in adult AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	PFS % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Powles *et al*, 1980[69] (full paper)	1977–79	HDT + AlBMT [CTX (120), TBI]	C	50	0	22	28	67:37 2 years	NYR:21	–	0.28 (0.07–1.20) 2 years	–	–	$p < 0.025$	–	4:11	Short follow-up.
Appelbaum *et al*, 1988[70] (full paper)	1977–82	HDT + AlBMT [CTX (120), TBI (1000–1575 rad)]	C (2 cycles) I (2 cycles) ± M	90	4	43	43	51:40 2 years 40:29 4 years	15:20	$p = 0.70$	0.63 (0.21–1.91) 2 years 0.60 (0.19–1.92) 4 years	46:24 2 years 40:21 4 years	11:13	$p = 0.26$	0.36 (0.11–1.16) 2 years 0.42 (0.13–1.39) 4 years	–	Authors imply that all patients with a potential donor were typed. Control patients were randomised to receive I or I + M. Patients were excluded (one from CC arm, three from HDT arm) if they were not potentially fit enough to receive a transplant.
Champlin *et al*, 1985[71] (full paper)	1979–83	HDT + AlBMT [CTX (120), TBI (10–11.25 Gy)]	C	67	0	23	44	47:43 2 years 40:27 4 years	21:19	$p > 0.4$	0.83 (0.22–3.12) 2 years 0.58 (0.14–2.40) 4 years	–	–	–	–	9:4	Patients in the HDT arm were all aged ≤ 45 years. All patients aged > 45 years were included in the CC arm. Authors comment that HDT decreases the number of leukaemia-related deaths but increases the number of procedure-related deaths.
Hewlett *et al*, 1995[72] (full paper)	1982–86	HDT + AlBMT [CTX (120), TBI (12 Gy)]	C (2 cycles) I (2 cycles) ± M (2 years)	165	2	34[a]	110	–	–	–	–	50:35 2 years[b] 42:30 4 years[b]	24:16	$p = 0.43$[c]	0.55 (0.23–1.32) 2 years 0.55 (0.22–1.37) 4 years	–	[a] Plus 19 matched but not given a transplant. Data are split BMT vs. donor no BMT vs. no donor. To calculate the ORs the total number of events = no. among patients who received a transplant + no. among patients matched but not given a transplant. [b] Matched but did not receive a transplant: PFS = 47% at 2 years; 42% at 4 years. [c] Donor vs. no donor.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*
DFS = disease-free survival. Superscript letters cross-reference to comments column.
The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 27 contd *CCTs comparing HDT/allogeneic PCT with conventional therapy in the consolidation of first remission in adult AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	PFS % HDT:CC	Median (months) HDT:CC	Statistics in paper	Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Conde *et al*, 1988[68] (full paper)	1982–86	HDT + AlBMT [CTX (120), TBI]	C (4 courses)	27	0	14	13	–	–	–	–	70:45 2 years	NYR:12	NS	0.36 (0.05–2.65) 2 years	3:–[d]	A combination of adult and paediatric patients. Authors comment that the CC results are poor. [d] For patients aged < 45 years.
Schiller *et al*, 1992[73] (full paper)	1982–90	HDT + AlBMT [Various]	C (1–3 cycles)	82	0	28	54	55:73 2 years 55:61 4 years	42:NYR	$p = 0.07$	2.77 (0.77–9.98) 2 years 1.36 (0.41–4.56) 4 years	–	–	–	–	9:2	More patients in the CC arm were known to have cytogenetic abnormalities. High no. of treatment-related deaths in the HDT arm. Authors conclude larger studies are needed to identify patients with poor prognosis who might benefit from HDT.
Labar *et al*, 1991[74] (abstract)	1983–90[e]	–	–	220	–	70	150	58:5 3 years	–	–	0.04 (0.02–0.11) 3 years	–	–	–	–	–	Poorly reported study. [e] Adults.
Cassileth *et al*, 1990[75] (full paper)	1984–88														–	–	The DFS is given as HDT vs. C vs. M. [f] All exclusions are from the HDT arm.
Comparison 1		–	M (2 years)	–		48	22	–	–	–	–	40:14 2 years	17:7	$p = 0.09$	0.24 (0.06–1.01) 2 years	–:0	
Comparison 2		–	C (10 days)	–		48	28	–	–	–	–	40:38 2 years	17:13	$p = 0.5$	0.99 (0.28–3.43) 2 years	–:2	
Overall results		–	–	103	5[f]	48	50	–	–	–	–	–	–	–	0.60 (0.26–1.38) 2 years	–	

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*
DFS = disease-free survival. Superscript letters cross-reference to comments column.
The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 27 contd *CCTs comparing HDT/allogeneic PCT with conventional therapy in the consolidation of first remission in adult AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Archimbaud *et al*, 1994[60] (full paper)	1985–90	HDT + AlBMT [CT + TBI or CTX + BU]	C	58	0	27	31	55:57 2 years 47:45 4 years	30:40	NS	1.11 (0.28–4.30) 2 years 0.89 (0.23–3.42) 4 years	51:33 2 years 47:27 4 years	24:13	NS	0.45 (0.12–1.77) 2 years 0.39 (0.10–1.57) 4 years	6:3	Authors imply that patients were tissue typed before induction therapy started. Survival figures reported as time from diagnosis. Authors conclude that there is no benefit for HDT and suggest that better prognostic factors are needed.
Dinsmore *et al*, 1987[76] (abstract)	–	HDT + AlBMT [CTX, TBI (1000–1320 rad)]	ANC + CYT + 6TG	39	0	17	32	65:63[g]	–	–	–	58:50[g]	–	–	–	4:–	[g] At time of analysis. Survival and PFS figures are crude not actuarial percentages. Authors note that there have been fewer relapses in the HDT arm, but the treatment related death rate is high.
Trial comparing donor vs. no donor																	
Burnett *et al*, 1994[66] (abstract)	1988–94	C (2 cycles) HDT + AlBMT	C (2 cycles) Either HDT + ABMT or NFT	–	–	299 (donor)	467 (no donor)	58:51[h]	–	$p = 0.7$	–	–	–	–	–	19%:–	Includes adults and children. (Analysis of paediatric patients alone is in *Table 17*.) Control patients received either an autologous BMT or NFT. Comparison for patients aged ≤ 45 years. [h] Only patients aged ≤ 45 years included. Authors conclude that there is no evidence of a benefit for those patients with a matched donor. Patients of all ages included in the total patient numbers; survival information is only for patients aged ≤ 45 years.

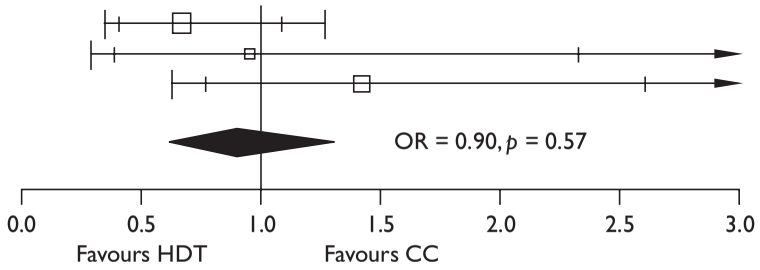
* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

DFS = disease-free survival. Superscript letters cross-reference to comments column.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 28 *RCTs comparing HDT/autologous transplantation with CC for the consolidation of first remission in adult AML: 4-year survival*

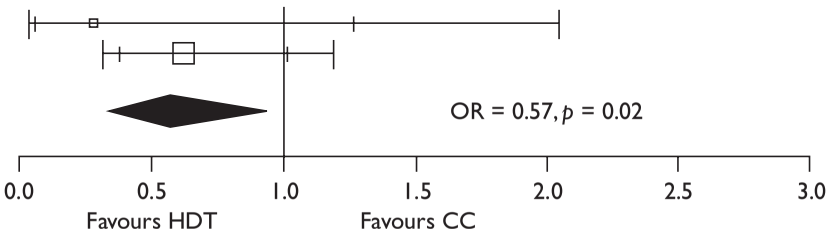
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Zittoun *et al*, 1995[63]	56/128	68/126	–6.49	15.93	
Reiffers *et al*, 1993[64]	17/39	17/38	–0.22	4.81	
Harousseau *et al*, 1996[65]	45/86	34/78	3.57	10.27	
Total…	118/253	119/242	–3.14	31.01	



OR = 0.90 (95% CI 0.64–1.29) $\chi^2_{(1)} = 0.32, p = 0.57$ Het$\chi^2_{(2)} = 3.58, p = 0.17$

TABLE 29 *RCTs comparing HDT/autologous transplantation with CC for the consolidation of first remission in adult AML: 2-year PFS*

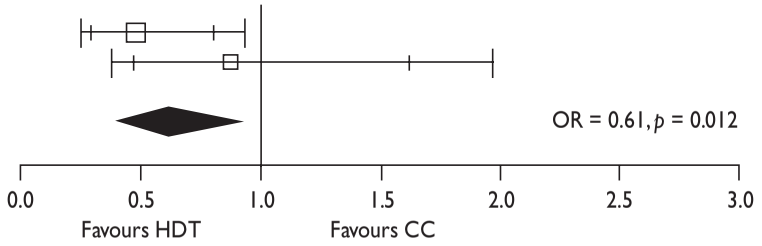
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Reiffers *et al*, 1989[62]	9/15	17/20	–2.14	1.69	
Zittoun *et al*, 1995[63]	64/128	78/126	–7.56	15.71	
Total…	73/143	95/146	–9.70	17.40	



OR = 0.57 (95% CI 0.36–0.93) $\chi^2_{(1)} = 5.34, p = 0.02$ Het$\chi^2_{(1)} = 0.95, p = 0.33$

TABLE 30 *RCTs comparing HDT/autologous transplantation with CC for the consolidation of first remission in adult AML: 4-year PFS*

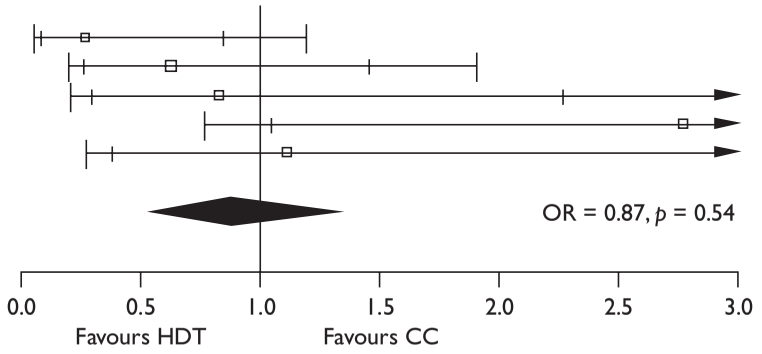
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Zittoun *et al*, 1995[63]	67/128	88/126	–11.10	15.16	
Harousseau *et al*, 1996[65]	50/86	48/78	–1.39	9.90	
Total…	117/214	136/204	–12.50	25.06	OR = 0.61, p = 0.012



OR = 0.61 (95% CI 0.41–0.90) $\chi^2_{(1)}$ = 6.24, p = 0.012 Het$\chi^2_{(1)}$ = 2.10, p = 0.15

TABLE 31 *CCTs comparing HDT/allogeneic transplantation with CC for the consolidation of first remission in adult AML: 2-year survival*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Powles *et al*, 1980[69]	7/22	18/28	–4.00	3.14	
Appelbaum *et al*, 1988[70]	21/43	26/43	–2.50	5.39	
Champlin *et al*, 1985[71]	12/23	25/44	–0.70	3.79	
Schiller *et al*, 1992[73]	13/28	13/54	4.12	4.04	
Archimbaud *et al*, 1994[60]	12/27	13/31	0.36	3.60	
Total…	65/143	95/200	–2.72	19.97	OR = 0.87, p = 0.54

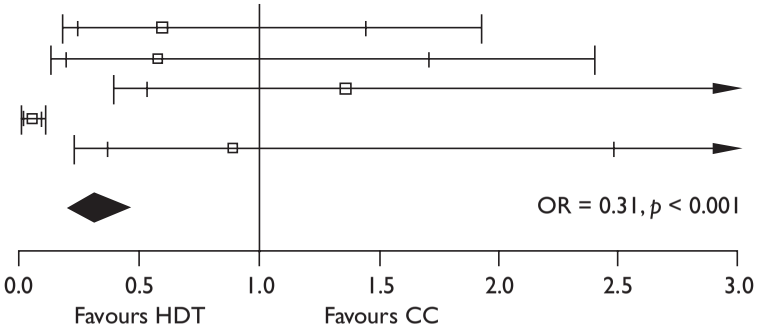


OR = 0.87 (95% CI 0.56–1.35) $\chi^2_{(1)}$ = 0.37, p = 0.54 Het$\chi^2_{(3)}$ = 10.25, p = 0.017

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 32 *CCTs comparing HDT/allogeneic transplantation with CC for the consolidation of first remission in adult AML: 4-year survival*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Appelbaum *et al*, 1988[70]	26/43	31/43	–2.50	4.86	
Champlin *et al*, 1985[71]	14/23	32/44	–1.79	3.30	
Schiller *et al*, 1992[73]	13/28	21/54	1.39	4.53	
Labar *et al*, 1991[74]	29/70	143/150	–25.70	8.18	
Archimbaud *et al*, 1994[60]	14/27	17/31	–0.43	3.65	
Total…	96/191	244/322	–29.10	24.52	

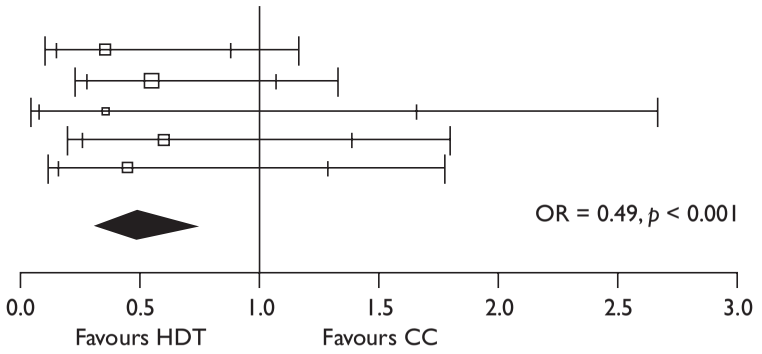


OR = 0.31 (95% CI 0.21–0.45) $\chi^2_{(1)} = 34.44, p < 0.001$ Het$\chi^2_{(4)} = 49.23, p < 0.001$

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 33 *CCTs comparing HDT/allogeneic transplantation with CC for the consolidation of first remission in adult AML: 2-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Appelbaum *et al*, 1988[70]	23/43	33/43	–5.00	4.94	
Hewlett *et al*, 1995[72]	27/53	72/110	–5.19	8.58	
Conde *et al*, 1988[68]	4/14	7/13	–1.70	1.69	
Cassileth *et al*, 1990[75]	29/48	36/50	–2.84	5.53	
Archimbaud *et al*, 1994[60]	13/27	21/31	–2.83	3.56	
Total…	96/185	169/247	–17.60	24.30	

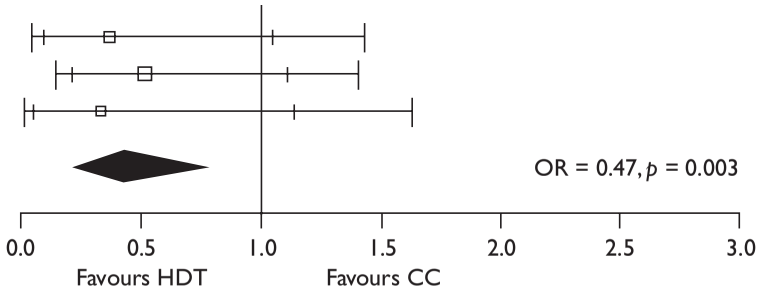


OR = 0.49 (95% CI 0.31–0.66) $\chi^2_{(1)} = 12.68, p < 0.001$ Het$\chi^2_{(4)} = 0.93, p = 0.92$

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 34 *CCTs comparing HDT/allogeneic transplantation with CC for the consolidation of first remission in adult AML: 4-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Appelbaum *et al*, 1988[70]	26/43	34/43	–4.00	4.59	
Cassileth *et al*, 1990[75]	30/53	77/110	–4.79	8.12	
Archimbaud *et al*, 1994[60]	14/27	23/31	–3.22	3.39	
Total…	70/123	134/184	–12.00	16.10	



OR = 0.47 (95% CI 0.29–0.77) $\chi^2_{(1)} = 8.95, p < 0.003$ Het$\chi^2_{(2)} = 0.41, p = 0.81$

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 35 *Cohort studies comparing HDT/allogeneic PCT and CC in the consolidation of first remission in adult AML*

Trial reference	Entry years	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Reiffers *et al*, 1989[62] (full paper)	1984–86	HDT + AIBMT [CTX (120), TBI (12 Gy)]	C (1 cycle) C (4 cycles) + cranial RT	43	0	23	20	–	–	61:16 2 years	–	4:0	Authors conclude that because of the poor results with CC regimens allogeneic transplantation is the best treatment for patients with AML in first remission.
Zittoun *et al*, 1995[63] (full paper)	1986–93	HDT + AIBMT [CTX (120), TBI (10–12 Gy)]	C (1 cycle) C (1 cycle)	294	0	168	126	59:66 2 years 59:46 4 years	NYR:31	56:38 2 years 55:30 4 years	NYR:18	29:9	Authors conclude that the advantage to transplantation is limited to PFS.
Reiffers *et al*, 1993[64] (full paper)	1987–90	HDT + AIBMT [CTX (120), TBI (2 Gy)]	C (1 cycle) C (5 cycles) M (2 years)	74	0	36	38	65:55 3 years	–	66.5:45 3 years	–	1:0	PFS did not include death from non-disease or treatment-related causes as an event. CC arm included patients of all ages; the allogeneic arm included only patients aged ≤ 45 years. Authors comment that they can make no firm conclusions regarding the comparative efficacy of the two treatment regimens.
Harousseau *et al*, 1996[65] (abstract)	1987–94	–	C (1 cycle) C (1 cycle)	–	–	–	78	51:57 4 years	–	38:42 4 years	–	–	It is unclear how many patients were in each arm of the trials. Authors conclude that allogeneic transplantation is not superior to CC.
Hubner *et al*, 1996[61] (full paper)	1988–91	HDT + AIBMT [CTX,TBI or BU, CYT]	C (1 cycle) C (1 or 2 cycles)	103	0	34	69	66:65 2 years 62:46 4 years	NYR:36	62:41 2 years 62:63 4 years	NYR:16	2:2	Chemotherapy cohort is a mixture of non-randomised and randomised patients. Paper is very poorly reported; not all analyses are ITT.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 36 *Cohort studies comparing HDT/allogeneic PCT with CC for the consolidation of second remission in AML*

Trial reference	Entry years	Study type	Treatment regimen		No. of patients			Survival		PFS		Toxic deaths HDT:CC	Comments
			HDT	CC	Total	HDT	CC	% HDT:CC	Median (months) HDT:CC	% HDT:CC	Median (months) HDT:CC		
Gale *et al*, 1996[77] (full paper)	1980–89	RCo	AlBMT [various therapies]	Various, all patients in trials	511	257	244	60:30	–	26:17 3 years	–	56%:7%	HDT patients from IBMTR database and CC patients entered into three chemotherapy trials. Subset analysis suggested BMT was beneficial in patients who were aged ≤ 30 years and with first remission > 1 year and in those who were aged > 30 years and with first remission ≤ 1 year. Includes paediatric and adult patients.
Gale *et al*, 1991[78] (abstract)	–	RCo	AlBMT [various therapies]	Various, all patients in trials	517	222	295	–	–	32:27 2 years	–	–	CC data were adjusted to reflect a time to treatment bias. Authors conclude that transplantation decreases the number of relapses. It is likely that some of these patients are included in the Gale *et al*, 1996[77] paper above. Includes paediatric and adult patients.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 37 *On-going RCTs and RCTs not yet reported in adult AML*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
MRC AML12	Open	AML	Induction [CYT, DNR/MTX, ETOP] Post-induction [AMSA, CTX, ETOP] Consolidation [3 or 4 cycles] followed by HDT + AIBMT/ABMT [TBI, CTX/MP]	Induction [CYT, DNR/MTX, ETOP] Post-induction [AMSA, CTX, ETOP] Consolidation [4 or 5 cycles]	2000†
DUT-HOVON-AML-4	Closed 01/01/90	AML	Induction [3 cycles including CYT, DNR, AMSA] Consolidation [MTX, ETOP] HDT + ABMT [BU, CTX]	Induction [3 cycles including CYT, DNR, AMSA] Consolidation [MTX, ETOP]	340
E-3489‡ EST-3489	Closed	AML	Induction [CYT, IDA] HDT + AIBMT/ABMT [BU, CTX]	Induction [CYT, IDA] Consolidation [CYT]	808

* *See list of abbreviations of drug names on page ii.*
† *Number at entry; not all will be randomised to BMT.*
‡ *PDQ trial reference code.*

Shaded boxes indicate open UK-based trials.

continued

TABLE 37 contd *On-going RCTs and RCTs not yet reported in adult AML*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
PCI-9153‡ NCI-V92-0090	Closed 16/05/94	AML for patients in first CR	Consolidation [MTX, ARA-C, DNR] HDT + ABMT (purged) [CTX, BU]	Consolidation [MTX, CYT, DNR]	104
BGMT-91	Closed	AML	HDT + AIBMT [CTX,TBI]	CC	–
Maximum planned accrual …					**> 3252§**

* *See list of abbreviations of drug names on page ii.*
‡ *PDQ trial reference code.*
§ *This number indicates the number of patients starting induction therapy; the number being randomised to HDT vs. CC is likely to be much lower.*

Chapter 8

Review: chronic myeloid leukaemia

Introduction

The natural history of untreated CML has been well described and includes an initial chronic phase, the median duration of which is about 3.5 years. Approximately 15% of cases transform to an acute phase (blast crisis) each year and this transformation is invariably followed rapidly by death, so that by 10 years from presentation most patients have died.[79]

The traditional aim of conventional therapy, which is generally relatively simple and involves oral administration of non-toxic drugs, has been to improve quality of life rather than to cure or prolong survival. Recently however, alpha-interferon has been reported to significantly increase the duration of the chronic phase.[80]

CML is primarily a disease of the elderly, the majority of whom would be unsuitable for HDT/PCT even if it were proved to be effective. There are, however, a number of younger patients who may be suitable for more intensive therapies including a small proportion in the 20–40 year age group who might be considered for allogeneic transplantation from either related or unrelated donors. On the basis of encouraging observations of long-term survival rates approaching 50% in case series and cohort studies, and despite the high mortality associated with these procedures, allogeneic transplantation from a sibling donor is accepted by many as the treatment of choice for young patients. There is a widely held belief that randomised comparisons of this approach with conventional approaches would be unethical. For older patients it is thought that the high early mortality associated with transplantation may outweigh the potential advantages of any possible long-term benefit and consequently HDT/PCT has been little tested or used for such patients.

Methods

The search strategies set out in chapter 2 were used.

Results

No RCTs or CCTs were found. Four cohort studies were identified (*Table 38*).

Discussion

There is at present no reliable evidence from RCTs or CCTs concerning the use of HDT involving either allogeneic or autologous transplantation in the treatment of CML. Treatment decisions are made largely in relation to the age and fitness of a patient, together with perceptions of a treatment's efficacy.

Given the poor prognosis and lack of alternative potentially curative therapies, allogeneic transplantation is widely accepted as routine therapy for young patients with a suitable sibling donor. However, in the absence of information from prospective controlled trials, it is impossible accurately to quantify the true magnitude of any potential benefit or associated risk of this treatment.

RCTs, or well conducted CCTs, are essential to evaluate reliably the therapeutic options currently available to patients with CML. Two trials that are currently on-going compare HDT/autologous transplantation with CC (*Table 39*) and participation in these trials should be encouraged.

TABLE 38 *Cohort studies comparing HDT/PCT with CC in CML*

Trial reference	Entry years	Study type	Time of HDT	Treatment regimen*		No. of patients			Survival	Toxic deaths HDT:CC	Comments
				HDT	CC	Total	HDT	CC	% HDT:CC		
Klingebiel *et al*, 1990[81] (full paper)	HDT: 1983–88 CC: 1983–88	RCo	Children with adult type CML: transplanted in first chronic phase or as soon as possible after diagnosis	HDT + AlBMT [BU or HYD]	HYD + BU-based regimens	35[a]	11 (AlBMT)	24	78:79 2 years 78:55 5 years	2:–	CC cohort was taken from registry data. Selection was based on the availability of full data. [a] Three of 14 HDT patients excluded.
ICSGCML, 1993[82] (full paper)	1984–88	PC	During first chronic phase	HDT + AlBMT [Majority CTX + TBI]	HYD + BU-based regimens	258	50 (AlBMT)	208	70:83 2 years 52:44 4 years	24:–	Patients in 55 Italian hospitals were registered at diagnosis, then followed up; no guidelines were given for treatment Patients who received transplants were significantly younger and there were more females in this group. Subgroup analysis suggested that for patients aged < 30 years BMT was better, although the authors give a warning regarding the weight placed on these results.
Hoyle *et al*, 1993[83] (abstract)	1984–92	RCo	During first chronic phase	HDT + autologous PBPCT	–	–	21 (ABMT)	–	–	–	Comparison of patients who received transplants at Hammersmith hospital with age-matched controls from the MRC CML database. Seven HDT patients survived > 7 years. Authors report a significant advantage for autografted patients.
Gale *et al*, 1994[84] (abstract)	–	RCo	During chronic phase	HDT + AlBMT [Various – registry data]	HYD- or interferon-based regimens	2152	1846 (AlBMT)	306	–	–	The cohorts were heavily imbalanced; the comparisons were made following adjustments. There was a survival advantage for CC in the first years after diagnosis; later transplant recipients fared better. HDT cohort was taken from the IBMTR; CCs were from an RCT.

* *See list of abbreviations of drug names on page ii.*
Superscript letters cross-reference to comments column.
The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 39 *On-going RCTs in CML*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
GER-CML-3 EU-95042†	Open	CML	HU, alpha-interferon HDT + ABMT/PBPCT [IDA, CYT]	HU, alpha-interferon	750
MRC-LEUK-CML-IV EU-96029†	Open	CML	HU, alpha-interferon HDT + ABMT/PBPCT [IDA, CYT]	HU, alpha-interferon	800
Maximum planned accrual ...					**1550**

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*
Shaded box indicates open UK-based trial.

Chapter 9

Review: chronic lymphocytic leukaemia

Introduction

Chronic lymphocytic leukaemia (CLL) is primarily a disease of the elderly, and as the overall median survival is between 8 and 12 years, death often occurs due to other causes. Therefore, it is difficult to justify the use of HDT/PCT in this population. Treatment for this condition in its early stages normally consists of initial observation followed by chemotherapy often involving the oral administration of a single alkylating agent such as chlorambucil, which is aimed at improving symptoms rather than at cure. There are, however, a minority of younger patients who may benefit from and be suitable for more intensive therapies.

Methods

The search strategies set out in chapter 2 were used.

Results

No trial or comparative study of HDT/PCT versus CC in CLL was identified.

Discussion

HDT/PCT procedures have been little used or investigated in the treatment of CLL. Since the vast majority of patients are elderly, it is unlikely that HDT/PCT could have widespread applicability and its potential use is likely to be restricted to the small proportion of young patients.

It has recently been reported that the chemotherapeutic agent fludarabine appears to induce complete responses relatively easily and that HDT with autologous transplantation may have a role in improving survival for those patients who have responded to treatment. This hypothesis has yet to be tested and as far as is known no randomised trials are planned. It is also possible that the use of allogeneic support which could potentially harness the GVL approach may be of benefit in treating CLL, but even registry data on this approach are limited.

Currently, whilst likely to be feasible and potentially applicable to a small subset of patients, HDT/PCT remains an experimental approach to treating CLL. It is essential that if preliminary studies show HDT/PCT to be of potential benefit, the therapy should be tested in well-designed, conducted and analysed RCTs. Such trials would undoubtedly require national and international cooperation.

Chapter 10

Review: non-Hodgkin's lymphoma

Introduction

The non-Hodgkin's lymphomas (NHLs) are a relatively rare, clinically and pathologically heterogeneous group of malignant diseases of lymphoid tissue. On the basis of their pathological characteristics and clinical behaviour, they are usually divided into three major subgroups, termed low-, intermediate-, and high-grade NHL.

Low-grade NHLs are indolent diseases, with a characteristic relapsing and remitting course, and there is a median survival of 8 to 10 years from the time of diagnosis.[85a] Although low-grade NHLs are generally regarded as incurable, there have been very few studies addressing the use of HDT/PCT in the treatment of these diseases.

In contrast, HDT/PCT has been used widely for the treatment of intermediate- and high-grade NHLs. These are much more aggressive malignant diseases, in which modern first-line combination chemotherapy regimens produce complete response rates of about 60–80%.[85b] However, only 40–50% of patients achieve long-term disease-free survival.[85b] For those patients with relapsed or refractory disease, outcome is very poor, with only 10–15% achieving long-term disease-free survival after treatment with conventional second-line regimens.[86a] In early, registry-based and single-institution studies long-term PFS rates of 30–40% were reported for patients with relapsed/refractory disease treated with HDT/PCT. As a result, the use of HDT/PCT in this situation has become widespread.

Although the use of HDT/PCT was initially restricted to salvage in patients with poor prognosis, it has been applied more recently as post-remission therapy after conventional dose remission-induction treatment, and as a component of the initial induction therapy. The earlier use of HDT/PCT in these diseases has been due both to the increasing safety and reduced mortality of HDT/PCT which is associated with improved supportive care (particularly the use of peripheral blood stem cells) and the identification of high-risk patients with NHL (based on the International Index[86b]) which allows early intensification of therapy to be tested prospectively in high-risk patients.

Methods

The methods set out in chapter 2 were used. Seven RCTs and no CCTs were identified. As the RCTs treated patients in a variety of different disease stages, data from other cohort studies were also tabulated.

Results

RCTs comparing HDT/PCT with CC in NHL

A total of seven RCTs including 1292 patients were identified (*Table 40*); patients were randomised between 1987 and 1995. These RCTs included trials investigating HDT/PCT in a variety of different disease stages which were considered to be clinically distinct groups of patients who are generally managed differently and so each is considered separately.

First-line induction therapy

One paper,[87] and two abstracts presenting preliminary results,[88,89] reported trials which randomised a total of 524 patients to HDT/PCT as first-line therapy. One study[87] randomised to immediate HDT/PCT versus delayed HDT/PCT on relapse.

Survival

The full paper[87] reported no evidence of a difference between treatment arms. One of the abstracts[89] reported a significant benefit for CC. The other abstract[88] presented no summary statistics but stated that the results showed no advantage for HDT/PCT; the calculated OR at 3 years of 0.95 (99% CI 0.36–2.53) showed no evidence of a difference between the two treatments.

No combination of data at 2 years was possible (*Table 41*). Combining the results at 3 and 4 years gives a pooled result which shows no clear evidence of a difference between HDT/PCT and CC with an OR of 0.74 (95% CI 0.42–1.31) in favour of HDT/PCT (*Table 42*).

PFS

One publication[87] reported a significant PFS benefit for HDT/PCT and another[89] reported

a significant benefit for the CC arm. The third publication[88] presented no information on PFS. No combination of data was possible.

Consolidation of first complete remission

One full paper[90] reported a trial of HDT/PCT as consolidation of first complete remission which included 541 patients classified as poor risk according to the Coiffier criteria.

Survival

There was no evidence of a difference in survival between HDT/PCT and CC, with a reported relative risk of 1.03.

PFS

No evidence of a difference in PFS between HDT/PCT and CC was reported (relative risk = 1.19).

Consolidation of first remission in slow responders

Two full papers[91,92] reported trials investigating HDT/PCT as consolidation of first remission in patients who were slow responders to induction chemotherapy, which in total randomised 118 patients. Both papers presented survival and PFS curves.

Survival

Neither paper reported evidence of a difference in survival. The pooled ORs of 1.08 (95% CI 0.47–2.45) at 2 years (*Table 41*) and 1.73 (95% CI 0.80–3.75) at 4 years (*Table 42*) indicate no clear evidence of a difference between treatments, although both favour CC.

PFS

Neither trial showed evidence of a difference in overall PFS. Although both the combined 2-year OR of 0.84 (95% CI 0.40–1.73; *Table 43*) and the 4-year OR of 0.96 (95% CI 0.47–1.99; *Table 44*) favour HDT/PCT, they do not reach conventional levels of significance.

Consolidation of second or third complete or partial remission

One trial[93] of 109 patients investigated the use of HDT/PCT as consolidation of second or third complete or partial remission. This was reported in a full paper which presented survival and PFS curves.

Survival

The paper reported a significant survival advantage of HDT/PCT, although it was noted that a greater number of patients received radiotherapy in the HDT/PCT arm than in the CC arm (40% vs. 22%).

PFS

A significant advantage of HDT/PCT was also reported for PFS.

Cohort studies

Data from cohort studies are summarised in *Table 45*.

Discussion

High-grade and intermediate-grade lymphomas

Salvage therapy

HDT/PCT is now widely regarded as 'standard' treatment for patients with relapsed or refractory aggressive NHL. This is based largely on the results of retrospective studies from single institutions and transplant registries. More recently, this view has been supported by results from the single RCT[93] discussed above, which reported an advantage in survival and PFS for HDT/PCT over CC in patients treated in second or third remission. The trial took 7 years to complete, and only 109 patients were randomised, although the original target accrual was for 142 randomised patients.[94]

No other on-going or planned prospective studies address the role of HDT/PCT in the salvage setting. Therefore, on the basis of results from only one small trial, HDT/PCT is now regarded by many as the optimum salvage therapy for aggressive NHL. Further prospective randomised studies are required to establish reliably whether or not HDT/PCT is superior to conventional dose salvage treatment. As far as is known, no such trials are currently planned.

First-line therapy in previously untreated patients

Three randomised studies have been reported, two of which were in abstract form. The trial[87] reported as a full paper found a significant improvement in PFS in the HDT/PCT arm which was not observed in the results for overall survival. The other two reports[88,89] are very preliminary. Consequently, at present there is insufficient published evidence to determine the role of HDT/PCT in this situation.

Consolidation of first complete remission

A single randomised study has addressed the role of HDT/PCT in complete remission, for patients with high-risk aggressive NHL defined using prognostic factors similar, but not identical, to those

identified by the International Index. No difference in overall survival or PFS was reported. However, in a later subgroup analysis, published since the completion of this review, the authors reported an improved PFS and overall survival for patients defined as high-intermediate- or high-risk according to the International Index.

There are several randomised trials in progress (*Table 46*) which compare high-dose with conventional dose post-remission therapy for patients with high-risk disease. All have very similar study designs, and most will be completed within the next 1 to 2 years.

Consolidation of first partial remission in slowly responding patients

Two randomised trials, both with small numbers, assessed the role of HDT/PCT in slowly responding patients, who have been shown in several retrospective studies to have a poor prognosis. Both trials were small, and both failed to demonstrate a clear difference in overall survival or PFS between treatment arms.

Low-grade lymphomas

There is very little evidence at present on the role of HDT/PCT in low-grade lymphoma. One randomised study has recently closed because of poor accrual, and other studies are on-going. Participation in randomised trials should be encouraged.

In summary, most clinical trials in NHL have focused on intermediate- and high-grade disease. There are very few randomised trials currently reported, and no definitive conclusions can be made about the efficacy of HDT/PCT.

In the absence of further randomised trials, the use of HDT/PCT as salvage therapy is likely to remain a standard approach. Its role as initial therapy, either for untreated patients or for those in remission after conventional dose induction therapy, remains uncertain, but this may be clarified on completion of the on-going prospective trials (*Table 46*). Participation in these trials should be encouraged.

TABLE 40 *RCTs comparing HDT/PCT with CC in NHL*

Trial reference	Entry years	Disease eligibility	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
First-line therapy																	
Gianni *et al*, 1997[87] (full paper)	1987–93	Diffuse large-cell, poor risk, LNH-87 criteria	ADR,VCR, PDN HDT + ABMT [CTX, VCR, MTX, ETOP, L-PAM,TBI (10–12.5 Gy)]	MACOP-B + delayed HDT	98	48	50	81:71 2 years 81:68 4 years	NYR: NYR	p = 0.09	0.60 (0.18–2.04) 2 years 0.50 (0.15–1.65) 4 years	81:58 2 years 81:58 4 years	NYR:62	p = 0.004	0.34 (0.11–1.04) 2 years 0.34 (0.11–1.04) 4 years	4:3	Crossover design; HDT given to all failing patients. Authors conclude advantage for HDT arm. Three secondary cancers (two in HDT arm, one in CC arm).
Santini *et al*, 1997[88] (abstract)	1992–95	Stage II–IV, poor prognosis, ≥ 1 –ve factors	HDT + AMBT [VACOP-B intensified]	VACOP-B + more CC if CR not attained	124	63	61	67:65 3 years	–	–	0.95 (0.36–2.53) 3 years	–	–	–	–	–	Interim results. Authors state results show no advantage of HDT.
Gisselbrecht *et al*, 1996[89] (abstract)	1993–94	Int/high grade ≥ 2 –ve factors	HDT + ASCT BEAM	ACVB	302	–	–	61:73[a]	–	p = 0.01	–	48:57[a]	–	p = 0.02	–	3.5%: 3.5%	[a] At median follow-up at 16 months. Abstract. Very short follow-up.
Consolidation of first CR																	
Haioun *et al*, 1997[90] (full paper)	1987–93	Int/high grade, ≥ 1 –ve factor	ACBV or NCVB HDT + ABMT [MTX (6000) + CBV]	ACBV or NCVB MTX, IFOS, ETOP, ASP, CYT (2 cycles)	541	268	273	69:67 5 years	NYR	RR = 1.03 p = 0.8	0.91 (0.57–1.47) 5 years	67:63 2 years 63:59 4 years	NYR:NYR	RR = 1.19 p = 0.2	0.83 (0.52–1.33) 2 years 0.84 (0.54–1.33) 4 years	2:1	CC dose is intensive compared with more widely used regimens. Authors conclude trial did not demonstrate advantage of HDT.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated. HDT regimens (max dose, mg/m^2 unless otherwise stated) – BEAC: BCNU (300), ETOP (800), CYT (800), CTX (140/kg); CBV: CTX (6000), BCNU (300), ETOP (1000); VACOP-B: CTX (7000), VCR (140), MTX (8000), ETOP (2000); BEAM: BCNU (300), ETOP (200), CYT (200), MELP (140); ACBV = ADR + CBV; NCBV = MTOX + CBV. CC regimens – MACOP-B = MTX, ADR, CTX, VCR, PRED, BLM; VACOP-B = CTX, VCR, MTX, ETOP; F-MACHOP = FU, MTX, CYT, CTX, ADR, VCR, PRED; CHOP = CTX, ADR, VCR, PRED; DHAP = DMS, CACP, CYT; ACVB = CTX, EPI, VDR, PRED, BLM.*

Superscript letters cross-reference to comments column. HR = hazard ratio; Int = intermediate; WF = working formulation.

continued

TABLE 40 contd *RCTs comparing HDT/PCT with CC in NHL*

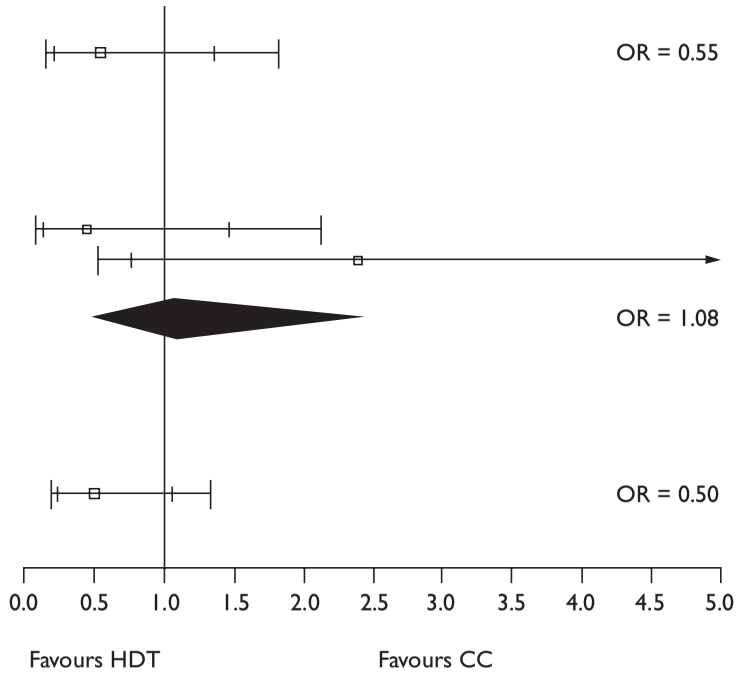
Trial reference	Entry years	Disease eligibility	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Consolidation of first remission in slowly responding patients																	
Martelli *et al*, 1996[91] (full paper)	1988–91	Aggressive WF G, H, J and anaplastic large cell, pleomorphic T-cell	F-MACHOP or MACOP-B HDT + ABMT [BEAC ± RT]	F-MACHOP or MACOP-B DHAP (6 cycles) ± RT	49	22	27	77:59 2 years 73:59 4 years	NYR	NS	0.45 (0.09–2.14) 2 years 0.56 (0.12–2.61) 4 years	73:52 2 years 73:52 4 years	NYR	NS	0.42 (0.09–1.90) 2 years 0.42 (0.09–1.90) 4 years	0:0	Presence of mediastinal mass at diagnosis found to be a positive prognostic factor, and was imbalanced in the two study arms. Analysis of these patients alone also showed no difference between HDT and CC. Authors conclude that they are unable to determine whether HDT is superior to standard salvage therapy.
Verdonck *et al*, 1995[92] (full paper)	1987–94	Int/high grade, WF D-H	CHOP (4 cycles) HDT + ABMT [CTX (120 mg/kg), TBI (800 cGy)]	CHOP (4 cycles) CHOP (5 cycles)	69	34	35	71:85 2 years 56:85 4 years	NYR	HR = 2.2 95% CI 0.85–5.9 p = 0.12	2.4 (0.54–10.71) 2 years 4.17 (1.07–16.24) 4 years	50:57 2 years 43:53 4 years	22:NYR	HR = 1.3 95% CI 0.66–2.61 p = 0.43	1.33 (0.39–4.57) 2 years 1.68 (0.49–5.77) 4 years	2:0	Authors conclude HDT does not improve outcome in this group of slow responders.
Consolidation of second or third CR/PR																	
Philip *et al*, 1995[93] (full paper)	1987–94	Relapsed (first or second), Int/high grade	DHAP (2 cycles) HDT + ABMT [BEAC ± RT]	DHAP (2 cycles) DHAP (4 cycles) ± RT	109	55	54	64:47 2 years 61:38 4 years	NYR:18	p = 0.038	0.5 (0.19–1.34) 2 years 0.41 (0.15–1.11) 4 years	46:23 2 years 46:19 5 years	19:5	p = 0.001	0.36 (0.13–1.01) 2 years 0.29 (0.10–0.84) 4 years	4:0	Authors conclude trial shows significantly higher survival and PFS in relapsed chemosensitive NHL. Trial stopped early, due to slow accrual. 22/55 on HDT arm received RT whilst 12/54 on CC received RT.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated. HDT regimens (max dose, mg/m^2 unless otherwise stated) – BEAC: BCNU (300), ETOP (800), CYT (800), CTX (140/kg); CBV: CTX (6000), BCNU (300), ETOP (1000); VACOP-B: CTX (7000), VCR (140), MTX (8000), ETOP (2000); BEAM: BCNU (300), ETOP (200), CYT (200), MELP (140); ACBV = ADR + CBV; NCBV = MTOX + CBV. CC regimens – MACOP-B = MTX, ADR, CTX, VCR, PRED, BLM; VACOP-B = CTX, VCR, MTX, ETOP; F-MACHOP = FU, MTX, CYT, CTX, ADR, VCR, PRED; CHOP = CTX, ADR, VCR, PRED; DHAP = DMS, CACP, CYT; ACVB = CTX, EPI, VDR, PRED, BLM.*

Superscript letters cross-reference to comments column. HR = hazard ratio; Int = intermediate; WF = working formulation.

TABLE 41 *RCTs comparing HDT/autologous transplantation with CC in NHL: 2-year survival*

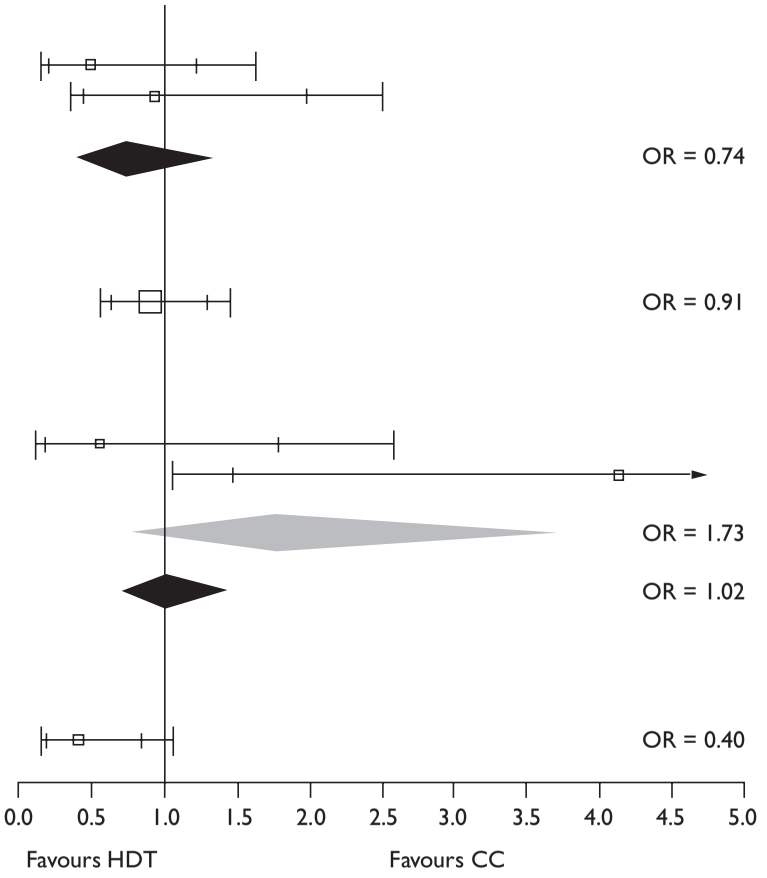
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
First-line therapy					
Gianni *et al*, 1997[87]	9/48	15/50	–2.76	4.58	OR = 0.55
Consolidation of first remission in slow responders					
Martelli *et al*, 1996[91]	5/22	11/27	–2.18	2.72	
Verdonck *et al*, 1995[92]	10/34	5/35	2.61	2.98	
Total…	15/56	16/62	0.43	5.70	OR = 1.08
Consolidation of second/third remission					
Philip *et al*, 1995[93]	20/55	29/54	–4.72	6.80	OR = 0.50



First-line therapy: OR = 0.55 (99% CI 0.16–1.83) $\chi^2_{(1)} = 1.66, p = 0.20$
First remission, slow responders: OR = 1.08 (95% CI 0.47–2.45) $\chi^2_{(1)} = 0.18, p = 0.67$ Het$\chi^2_{(1)} = 4.01, p = 0.04$
Second/third remission: OR = 0.50 (99% CI 0.19–1.34) $\chi^2_{(1)} = 3.28, p = 0.05$

TABLE 42 *RCTs comparing HDT/autologous transplantation with CC in NHL: 4-year survival*

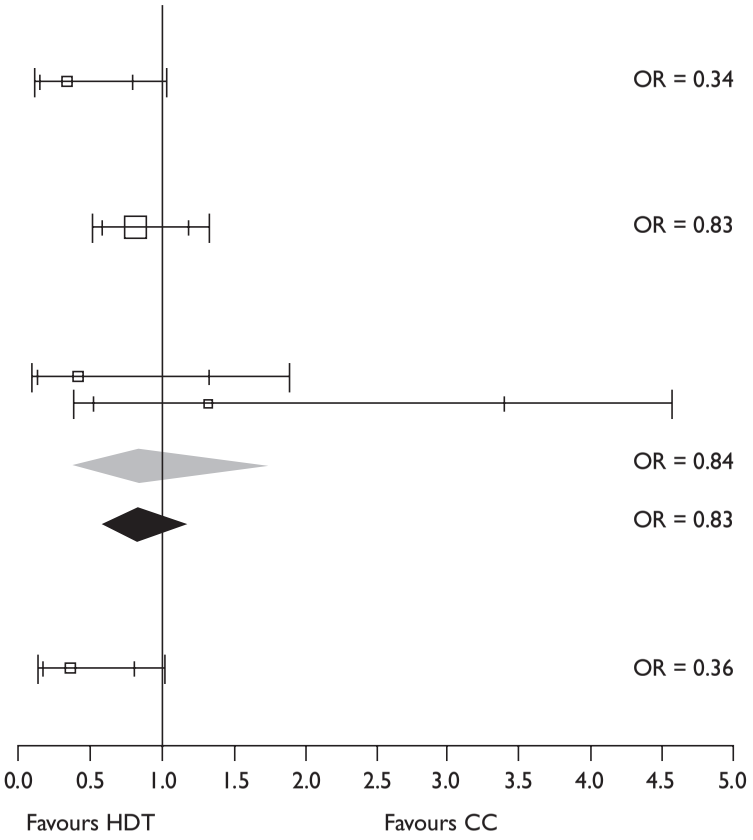
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
First-line therapy					
Gianni *et al*, 1997[87]	9/48	16/50	–3.24	4.70	
Santini *et al*, 1997[88]	21/63	21/61	–0.34	7.00	
Total, all first-line therapy …	30/111	37/111	–3.58	11.57	OR = 0.74
Consolidation of first remission (A)					
Haioun *et al*, 1997[90]	83/268	90/273	–2.70	29.47	OR = 0.91
Consolidation of first remission in slow responders (B)					
Martelli *et al*, 1996[91]	6/22	11/27	–1.63	2.80	
Verdonck *et al*, 1995[92]	15/34	5/35	5.14	3.60	
Sub-total ...	21/56	16/62	3.51	6.41	OR = 1.73
Total, all first remission (A + B) ...	104/324	106/335	0.81	35.88	OR = 1.02
Consolidation of second/third remission					
Philip *et al*, 1995[93]	21/55	33/54	–6.25	6.87	OR = 0.40



First-line therapy	OR = 0.74 (95% CI 0.42–1.31)	$\chi^2_{(1)} = 1.22, p = 0.27$	Het$\chi^2_{(1)} = 1.60, p = 0.21$
First remission (A):	OR = 0.91 (99% CI 0.64–1.31)	$\chi^2_{(1)} = 0.25, p = 0.61$	
First remission, slow responders (B):	OR = 1.73 (95% CI 0.80–3.75)	$\chi^2_{(1)} = 1.92, p = 0.16$	Het$\chi^2_{(1)} = 6.37, p = 0.01$
All first remission (A + B):	OR = 1.02 (95% CI 0.74–1.42)	$\chi^2_{(1)} = 0.18, p = 0.67$	Het$\chi^2_{(2)} = 8.53, p = 0.003$
Second/third remission:	OR = 0.40 (99% CI 0.15–1.08)	$\chi^2_{(1)} = 5.69, p = 0.02$	

TABLE 43 *RCTs comparing HDT/autologous transplantation with CC in NHL: 2-year PFS*

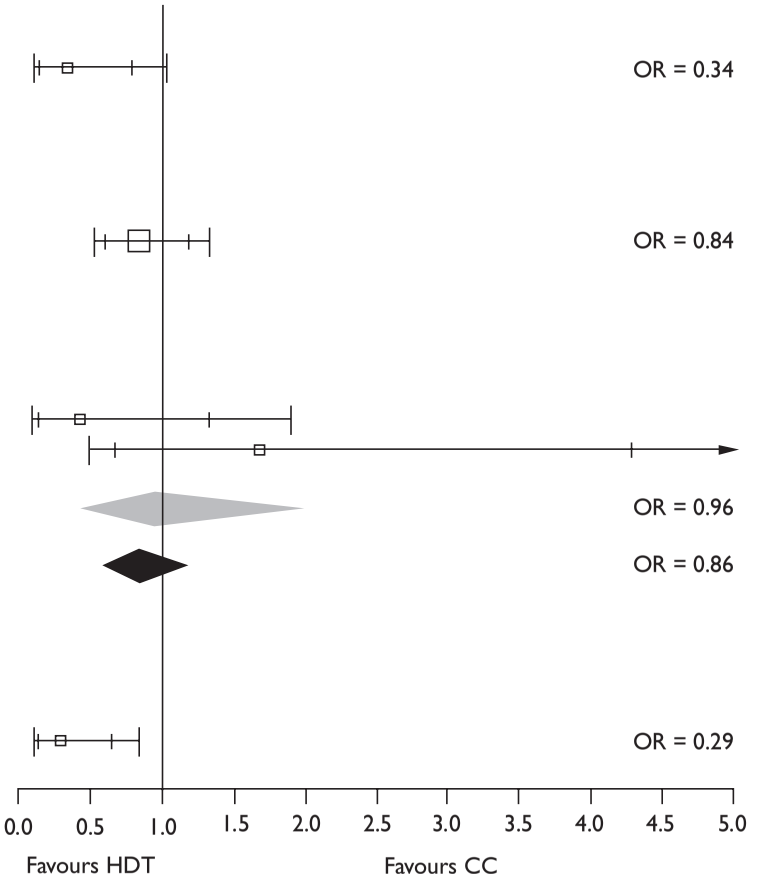
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
First-line therapy					
Gianni *et al*, 1997[87]	9/48	21/50	–5.69	5.26	OR = 0.34
Consolidation of first remission (A)					
Haioun *et al*, 1997[90]	88/268	101/273	–5.63	30.80	OR = 0.83
Consolidation of first remission in slow responders (B)					
Martelli *et al*, 1996[91]	6/22	13/27	–2.53	2.94	
Verdonck *et al*, 1995[92]	17/34	15/35	1.23	4.35	
Sub-total ...	23/56	28/62	–1.30	7.29	OR = 0.84
Total, all first remission (A + B) ...	111/324	129/335	–6.93	38.09	OR = 0.83
Consolidation of second/third remission					
Philip *et al*, 1995[93]	30/55	42/54	–6.33	6.17	OR = 0.36



First-line therapy	OR = 0.34 (99% CI 0.11–1.04)	$\chi^2_{(1)} = 6.15, p = 0.01$	
First remission (A):	OR = 0.83 (99% CI 0.52–1.33)	$\chi^2_{(1)} = 1.03, p = 0.31$	
First remission, slow responders (B):	OR = 0.84 (95% CI 0.40–1.73)	$\chi^2_{(1)} = 0.23, p = 0.63$	$\text{Het}\chi^2_{(1)} = 2.30, p = 0.13$
All first remission (A + B):	OR = 0.83 (95% CI 0.67–1.15)	$\chi^2_{(1)} = 1.26, p = 0.26$	$\text{Het}\chi^2_{(2)} = 2.30, p = 0.31$
Second/third remission:	OR = 0.36 (99% CI 0.13–1.01)	$\chi^2_{(1)} = 6.49, p = 0.01$	

TABLE 44 *RCTs comparing HDT/autologous transplantation with CC in NHL: 4-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
First-line therapy					
Gianni *et al*, 1997[87]	9/48	21/50	–5.69	5.26	OR = 0.34
Consolidation of first remission (A)					
Haioun *et al*, 1997[90]	99/268	112/273	–5.52	32.23	OR = 0.84
Consolidation of first remission in slow responders (B)					
Martelli *et al*, 1996[91]	6/22	13/27	–2.53	2.94	
Verdonck *et al*, 1995[92]	20/34	16/35	2.26	4.37	
Sub-total ...	26/56	29/62	–0.27	7.30	OR = 0.96
Total, all first remission (A + B) ...	125/324	141/335	–5.79	39.54	OR = 0.86
Consolidation of second/third remission					
Philip *et al*, 1995[93]	30/55	44/54	–7.34	5.99	OR = 0.29



First-line therapy	OR = 0.34 (99% CI 0.11–1.04)	$\chi^2_{(1)} = 6.15, p = 0.01$	
First remission (A):	OR = 0.84 (99% CI 0.53–1.33)	$\chi^2_{(1)} = 0.95, p = 0.33$	
First remission, slow responders (B):	OR = 0.96 (95% CI 0.47–1.99)	$\chi^2_{(1)} = 0.32, p = 0.58$	Het$\chi^2_{(1)} = 3.34, p = 0.07$
All first remission (A + B):	OR = 0.86 (95% CI 0.63–1.18)	$\chi^2_{(1)} = 0.84, p = 0.36$	Het$\chi^2_{(2)} = 3.45, p = 0.18$
Second/third remission:	OR = 0.29 (99% CI 0.10–0.84)	$\chi^2_{(1)} = 8.99, p = 0.003$	

TABLE 45 *Cohort studies comparing HDT/PCT with CC in NHL*

Trial reference	Entry years	Disease eligibility	AMBT use	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival Median (months) HDT:CC	Survival % HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Da *et al*, 1994[95] (abstract)	1983–92	–	–	RCo	–	–	54[a]	24[a]	30[a]	–	53 at 9 years: 18 at 7 years	–	–	–	[a] Mixture of HD and NHL patients (see also chapter 11), and there is no indication how many are HD and how many NHL. See also *Table 48*.
Morel *et al*, 1994[96] (full paper)	HDT: 1986–92 CC: 1984–87	High-risk follicular lymphoma	Consolidation of first remission[b]	PH	ACVBP HDT + ABMT (purged) [BEAM ± RT]		40	26	14	36:–	86:75 3 years	76:40 3 years	–	1:–	[b] The paper compared two cohorts; one cohort received ACVBP as induction + HDT, the other received ACVBP + NFT. Patients were included regardless of whether or not they reached CR. No general agreement as to the criteria for high-risk follicular lymphoma. Transplant was purged. Authors conclude that RCTs are needed.
Pettengell *et al*, 1996[97] (full paper)	1988–93	High grade, poor prognosis as defined by Kiel classification	First-line therapy	RH	VAPEC-B (7 cycles) IFOS, CYT HDT + PBPCT [CTX (200), BU (16) ± RT]	VAPEC-B (11 cycles) + RT	67	33	34	31:68	64:35 2 years	61:35 2 years	NYR:9	2:1	PBSC were used as the source of progenitor cells. Authors conclude that RCTs are needed.

* *See list of abbreviations of drug names on page ii. ACVBP = ADR, CTX, VDS, BLM, PRED; BEAM (total dose, mg/m^2) = BCNU (300), ETOP (200), CYT (200), MELP (140); VAPEC-B = ADR, CTX, VCR, BLM, ETOP, PRED.*

Superscript letters cross-reference to comments column.

HD = Hodgkin's disease.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 46 *On-going RCTs and RCTs not yet reported in NHL*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
EORTC-20901†	Open	Adult intermediate- and high-grade NHL	ADR, TENI, CTX, PRED, VCR, BLM HDT+ ABMT/PBPCT [BCNU, ETOP, CYT, CTX, RT]	ADR, TENI, CTX, PRED, VCR, BLM, RT	300
Scottish and Newcastle Lymphoma Group, NHL V(a)	Open	High-grade malignant lymphoma (good index)	CHOP or VAPEC B HDT + PBPCT [L-PAM]	CTX, ADR, VCR, PRED or ADR, CTX, VCR, BLM, ETOP, PRED	51 patients entered to date
EORTC-20963† BNLI Hovon 35	Open	Stages II or IV follicular NHL	Induction therapy HDT + PBPCT [CTX, TBI] Interferon maintenance	Induction therapy Interferon maintenance	469
LY02 UKLG/ANZLG/ EBMT	Open	Poor risk intermediate/ high-grade NHL	HDT + ABMT	CTX, ADR, VCR, PRED	500
EBMT-ECUP	Closed (30/04/97)	Adult relapsed follicular NHL	CTX, ADR, VCR, PRED HDT + ABMT/PBPCT [CTX, TBI]	CTX, ADR, VCR, PRED	200

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*

Shaded boxes indicate open UK-based and EORTC trials.

continued

TABLE 46 contd *On-going RCTs and RCTs not yet reported in NHL*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
UKLG-LY01	Closed (30/04/97)	Adult lymphoblastic lymphoma	VCR, ADR, CTX, ASP, PRED, MTX, DNR, CYT, or CTX, ADR, VCR, PRED, ASP, MTX, RT HDT + ABMT/PBPCT [CTX,TBI or BCNU, ETOP, CTX, L-PAM]	VCR, ADR, CTX, ASP, PRED, MTX, DNR, CYT, or CTX, ADR, VCR, PRED, ASP, MTX, RT Maintenance	200
NCI-D78-017-142†	Closed (01/01/81)	NHL	HDT + ABMT/AlBMT [ADR, CTX,TBI] MTX, CYT, TG, MTX or DAC, VCR	ADR, CTX MTX, CYT, TG, MTX or DAC, VCR	28
DUT-KWF-CKVO-8518†	Closed (01/01/93)	Intermediate- and high-grade NHL	CTX, ADR, VCR, PRED HDT + ABMT [CTX,TBI]	CTX, ADR, VCR, PRED	240
MSKCC-89084† NCI-V89-0192	Closed (01/12/93)	Advanced low-grade NHL	PRED, MTX, ADR, CTX, ETOP NM, VCR, PCZ, PRED HDT + ABMT [CTX, ETOP, TBI]	PRED, MTX, ADR, CTX, ETOP NM, VCR, PCZ, PRED, RT	106
Maximum planned accrual...					**2785**

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*

Chapter 11

Review: Hodgkin's disease

Introduction

Hodgkin's disease (HD) is an uncommon lymphoid malignancy, with an incidence that peaks in young adults and again among older age groups. Until recently, treatment was determined almost entirely by the anatomical stage at presentation, although in recent years the identification of various prognostic factors has allowed a more 'risk-directed' approach. However, the stage at presentation remains a major determinant of therapy. For patients with early-stage disease, extended field radiotherapy has been standard treatment for many years, although chemotherapy is now gaining an increasing role.

The use of combination chemotherapy such as MOPP (mustine, vincristine, procarbazine, prednisone) for advanced stage HD is associated with response rates of 80–90%.[98] Long-term follow-up of patients treated with this regimen has shown that about 50% remain alive and disease-free at 20 years,[99] with most deaths being due to recurrent HD, although treatment-related complications are also an important cause of late deaths. Long-term complications of regimens based on alkylating agents such as MOPP include secondary malignancy (leukaemia, NHL and solid tumours), immunosuppression, and male and female infertility. In recent years, anthracycline-based chemotherapy regimens such as ABVD (doxorubicin, vincristine, bleomycin and dacarbazine) have largely replaced MOPP and related regimens as the standard treatments for advanced HD.[98] These regimens are thought to produce higher long-term PFS rates, and less long-term toxicity.

As with NHL, HDT with autologous PCT in HD has been used primarily for patients with relapsed disease. Although patients initially treated with radiotherapy can be very effectively salvaged with combination chemotherapy, the long-term PFS for patients who relapse after, or are refractory to, their first-line chemotherapy regimen is only 15–20%.[100] Studies from single institutions and registry-based studies have reported higher PFS rates for patients receiving HDT/PCT than have been reported for conventional dose salvage therapy, and the use of HDT/PCT as second-line chemotherapy for HD is now widely accepted.

Although studies of HDT/PCT to consolidate first remission are in progress, this approach has been limited by the difficulty in identifying 'poor-risk' patients with HD, in whom the long-term PFS is sufficiently poor to justify a more intensive approach.[101] It should be noted that young adults form a large proportion of the patients with HD, and therefore it is particularly important to evaluate the incidences of the potential long-term toxicities associated with HDT/PCT.

Methods

The methods set out in chapter 2 were used. One RCT and no CCTs were identified and so data from three other comparative studies were tabulated to provide supplementary qualitative information.

Results

RCT comparing HDT/PCT with CC in HD

The one RCT identified randomised resistant or relapsed HD patients[102] (*Table 47*). The trial was stopped early because of poor accrual, 40 of a planned 66 patients having been recruited.

Survival

No evidence of a difference in overall survival was reported.

PFS

A conventionally significant improvement in PFS was reported for the HDT/PCT arm.

Cohort studies

Data from cohort studies are summarised in *Table 48*.

Discussion

As with NHL, on the basis of retrospective data HDT/PCT is now generally considered as 'standard' therapy for patients with relapsed or refractory HD. Only one randomised trial has been published, and this is much too small to provide a basis for

firm conclusions. The paper[102] reported a significant improvement in PFS for HDT/PCT compared with conventional dose salvage therapy. No improvement in overall survival was observed, although this may be due in part to the fact that several patients who failed the conventional dose salvage therapy 'crossed over' to receive HDT/PCT. The trial is also confounded by the fact that a mixture of chemo-sensitive and chemo-resistant patients were included, and it is not apparent whether the two arms of the trial were balanced for these factors.

At present, HDT/PCT is generally accepted as a standard therapy for patients with HD which has relapsed after an initial combination chemotherapy regimen. However, further randomised trials are required to verify its role and recruitment into the on-going trial should be encouraged (*Table 49*).

The use of HDT/PCT to consolidate first remission in 'poor-risk' HD is the subject of at least two on-going trials (*Table 49*), but at present there is no published evidence to support its use.

TABLE 47 *RCT comparing HDT/PCT with CC in Hodgkin's disease*

Trial reference	Entry years	Disease eligibility	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Linch *et al*, 1993[102] (full paper)	–	Relapsed/ resistant	BEAM	Mini-BEAM	40	20	20	74:60 2 years	NYR:40	$p = 0.318$	0.51 (0.09–2.87) 2 years	59:21 2 years	50:8	$p = 0.025$	0.20 (0.04–1.02) 2 years	2:0	Heterogeneous patient group (i.e. resistant and relapsed); no indication if these characteristics were balanced between treatment groups. Some of initial (pre-trial) chemotherapy may have been inadequate by modern standards. Trial closed early due to difficulty in recruiting patients (recruited 40 out of target of 66). Four patients relapsing on CC were given HDT. Authors report PFS is significantly improved, with no significant difference in survival. They also state that follow-up is short. Also possible that patient groups were not balanced for previous RT. Sealed envelopes used for randomisation.

* *See list of abbreviations of drug names on page ii.*

BEAM (total dose, mg/m^2) = BCNU (300), ETOP (800), CYT (1600), L-PAM (140).

TABLE 48 *Cohort studies comparing HDT/PCT with CC in Hodgkin's disease*

Trial reference	Entry years	Disease eligibility	AMBT use	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Carella *et al*, 1991[103] (full paper)	HDT: 1983–90	Poor prognosis (stage IV Ann Arbour)	Consolidation of remission	PH	HDT + ABMT [CBV]	NFT	39	15	24	93[a]:	–	87:72 2 years 87:43 4 years	NYR:35	1:0	Poor risk factors used to select patients have not been substantiated in recent studies. [a] Crude survival not calculated from a Kaplan-Meier curve. Very little data on the control population. Authors state that they can draw no firm conclusions from this study.
Moreau *et al*, 1995[104] (abstract)	HDT: 1988 CC: 1980–88	Bulky or stage IV disease and partial response to first-line treatment	Consolidation of partial first response	PH	HDT + PBPCT [CBV + RT or BEAM ± RT or CTX (120), TBI (12 Gy)]	ABVD (3 courses) + RT (subtotal or total nodal irradiation)	109	18	91	100 at 43 months: 71 at 8 years	–	100 at 43 months: 66 at 8 years	–	–	PBPCT used. Authors state that in this selected group of patients HDT and transplantation may be of some benefit, but this needs to be confirmed in RCTs.
Da *et al*, 1994[95] (abstract)	1983–92	–	First-line therapy	RCo	–	–	54[b]	24[b]	30[b]	91 at 9 years: 20 at 7 years	–	–	–	–	[b] Mixture of HD and NHL patients (see also chapter 10). There is no indication how many are HD and how many NHL.

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated. ABVD = ADR, BLM, VBL, DAC; BEAM (total dose, mg/m^2) = BCNU (300), ETOP (800), CYT (1600), L-PAM (140).CBV (total dose, mg/m^2): CTX (6000), BCNU (450), ETOP (1000).*

Superscript letters cross-reference to comments column.

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 49 *On-going trials in HD*

Trial code	Disease eligibility	Treatment regimen*		Planned accrual
		HDT	CC	
HD01 EBMT and German Hodgkin's Disease Study Group	Relapsed disease, responding to chemotherapy	HDT + ASCT	ADR, BLM, VBL, DAC or other standard regimen	146
EBMT Lymphoma Working Party	First complete or good partial remission in patients with poor prognosis	HDT + ASCT	–	–
HD3 Scottish and Newcastle Lymphoma Group	First complete remission in 'poor prognosis' Hodgkin's disease	HDT + ABMT [L-PAM, ETOP]	VCR, ETOP, PCZ, CHL, ADR, VBL, BLM, PRED	150
Maximum planned accrual ...				**> 296**

* *See list of abbreviations of drug names on page ii.*

Shaded boxes indicate UK-based and EBMT trials.

Chapter 12

Review: multiple myeloma

Introduction

In spite of its reputation as a chemosensitive malignancy, multiple myeloma remains fatal for nearly all who contract it.[105] It is primarily a disease of the elderly and median survival is about 2–3 years,[106] during which time there is considerable morbidity, associated mainly with diffuse bone pain, resulting from the disease.

Alkylating agents (such as melphalan), given alone or with corticosteroids, have for many years been the mainstay of treatment, and when given appropriately are associated with few side-effects. About 55% of patients respond to chemotherapy[107] and a 'plateau' phase of stable disease associated with few symptoms is reached. Progression occurs in almost all patients and second-line treatment is at present unsatisfactory: responses are of short duration and there is a high morbidity associated with therapy. More aggressive combination therapies, aimed at increasing the duration of the initial plateau phase, have been introduced. These have had limited success and whether such intensive regimens, which are more difficult to administer and are associated with greater morbidity, have any benefit over melphalan and prednisolone is uncertain.[106,108]

The transient nature of remissions after conventional treatment has led to the investigation of dose intensification, especially for the younger patient population in whom such treatment can be tolerated. HDT with autologous support aims to induce a stable minimal disease state, if not a complete response. The duration of the plateau phase is possibly the most clinically important end-point in treating multiple myeloma, as this represents the period of time when the symptoms of the disease are best controlled and a patient's quality of life is best. Thus, even if HDT/PCT and CC were to be equally effective in terms of survival, if the PFS time is longer with HDT/PCT then it might become the treatment of choice for younger fitter patients.

Methods

The methods set out in chapter 2 were used. Only two RCTs and no CCTs were identified and so data from other comparative studies were also tabulated to provide supplementary qualitative information.

Results

RCTs comparing HDT/PCT with CC in multiple myeloma

The two RCTs identified reported on 357 randomised patients (*Table 50*). One trial[109] compared the use of HDT/PCT with CC as first-line treatment. The other[110] compared first-line HDT/PCT with deferred HDT/PCT for those patients with disease refractory to, or recurring after, CC. Patient recruitment over both trials occurred between 1990 and 1994. Both trials were reported as full papers with one[109] presenting survival and PFS curves.

Survival

A conventionally significant benefit for HDT/PCT over CC (*Table 50*) was reported for one trial.[109] No evidence of a survival difference was shown in the second trial.[110] At 2 years the combined OR of 0.68 (95% CI 0.42–1.10) favours HDT/PCT (*Table 51*).

PFS

One publication[109] reports a significant PFS benefit for HDT/PCT (*Table 50*). The other[110] makes no statistical comment. The calculated combined OR at 2 years (*Table 52*) suggests an absolute survival advantage for approximately 22% in favour of HDT/PCT with an OR of 0.39 (95% CI 0.25–0.59).

Cohort studies

Data from cohort studies are summarised in *Table 53*.

Discussion

Only two small RCTs were identified which compared HDT/autologous transplantation with conventional therapy. One trial[109] showed a small but significant improvement in both overall survival and PFS for HDT/PCT, despite appreciable attrition in the HDT/PCT arm with 26% of patients unable to complete the high-dose procedure as intended. A second trial[110] also showed an improvement in PFS with HDT/PCT, but no difference in

survival, possibly owing to the relatively large number of cross-overs to HDT/PCT in the conventional dose arm (32 of 79 patients). The combined ORs at 2 years suggested a PFS benefit for HDT/PCT, which was not seen in survival at this time. Because of the preliminary nature of the data from the trial by Fermand and colleagues,[110] combined ORs could not be calculated at 4 years, at which point the OR of the more mature trial by Attal and colleagues[109] suggests a benefit in favour of HDT/PCT.

At present, it is not possible to comment reliably on the efficacy of HDT/PCT with autologous transplantation compared with conventional therapy. Two trials are on-going (*Table 54*) and if the target accrual is reached the number of patients in randomised comparisons will be more than trebled. Participation in these trials should be encouraged.

The role of allogeneic transplantation for the treatment of multiple myeloma has been little investigated because of the age of the majority of patients and the very high early mortality which is thought to be greater than 40%.[111] At present allogeneic transplants are considered an experimental therapy.

TABLE 50 *RCTs comparing HDT/PCT with CC in multiple myeloma*

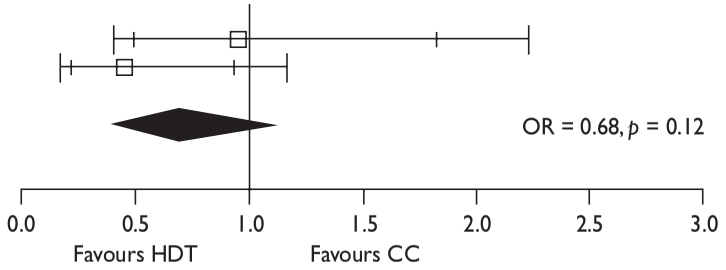
Trial reference	Entry years	Disease eligibility	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	Ex-cluded	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Attal *et al*, 1994[109] (full paper)	1990–93	Untreated stage II or III	VMCP + VBAP (4–6 cycles) HDT + ABMT [L-PAM, TBI] + Interferon	VMCP + VBAP (18 cycles) + Interferon	204	4[a]	100	100	77:76 2 years 59:39 4 years	NYR:37	$p = 0.03$	0.95 (0.40–2.23) 2 years 0.45 (0.22–0.93) 4 years	57:39 2 years 28:16 4 years	27:18	$p = 0.01$	0.49 (0.24–1.0) 2 years 0.50 (0.21–1.20) 4 years	7:5	[a] HDT, 2; CC, 2. 26% of HDT patients did not complete treatment. Nine CC patients crossed over. Authors comment HDT improves PFS and overall survival. Telephone randomisation.
Fermand *et al*, 1995[110] (full paper)	1990–94	Newly diagnosed, high tumour mass	CHOP (2 cycles) HDT + PBPCT [BCNU, ETOP, L-PAM, CTX, TBI]	CHOP (2 cycles) VMCP (6 cycles)	153	0	74	79	82:67 2 years	–	$p = 0.28$	0.45 (0.17–1.16)	77:47 2 years	–	–	0.28 (0.12–0.66)	5:–	A transplant was given to patients in the CC arm as rescue therapy or if they were resistant to primary VMCP. 32/79 CC patients crossed over. All patients were aged ≤ 55 years; older patients entered into a modified version of this trial.

* *See list of abbreviations of drug names on page ii. VMCP = VCR, L-PAM, CTX, PRED; VBAP = VCR, BCNU, ADR, PRED.*

Superscript letters cross-reference to comments column.

TABLE 51 *RCTs comparing HDT/autologous transplantation with CC in multiple myeloma: 2-year survival*

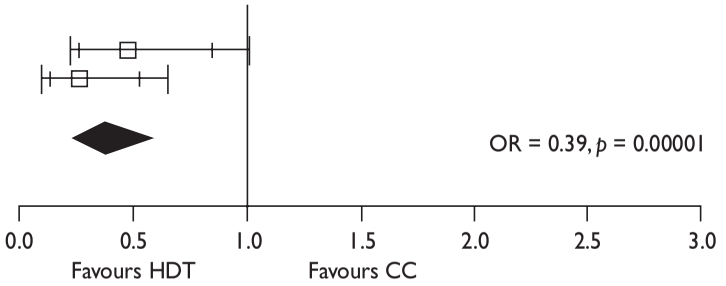
Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Attal *et al*, 1994[109]	23/100	24/100	–0.50	9.03	
Fermand *et al*, 1995[110]	13/74	26/79	–5.86	7.30	
Total ...	36/174	50/179	–6.36	16.34	OR = 0.68, p = 0.12



OR = 0.68 (99% CI 0.42–1.10) $\chi^2_{(1)}$ = 2.48, p = 0.12 Het$\chi^2_{(1)}$ = 2.26, p = 0.13

TABLE 52 *RCTs comparing HDT/autologous transplantation with CC in multiple myeloma: 2-year PFS*

Reference	No. events/no. entered HDT	CC	O – E	Variance	OR
Attal *et al*, 1994[109]	43/100	61/100	–9.00	12.54	
Fermand *et al*, 1995[110]	17/74	42/79	–11.50	9.11	
Total ...	60/174	103/179	–20.50	21.65	OR = 0.39, p = 0.00001



OR = 0.39 (99% CI 0.25–0.59) $\chi^2_{(1)}$ = 19.41, p = 0.00001 Het$\chi^2_{(1)}$ = 1.59, p = 0.21

TABLE 53 *Cohort studies comparing HDT/PCT with CC in multiple myeloma*

Trial reference	Entry years	Study type	Disease eligibility	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Alexanian *et al*, 1995[112] (full paper)	1985–93	RCo	Primary refractory disease	L-PAM + TBI or BU, CTX, TSPA HDT + ABMT/PBPCT + Interferon maintenance	–	102	41	61	–	–[a]	–[a]	–	3:–	All CC patients must have lived ≥ 3 months. Patients were denied HDT on socio-economic grounds. Subgroup analysis suggested patients with high or intermediate tumour mass treated within 1 year do better with HDT; no difference for low tumour mass. [a] Various curves presented by subgroup but no overall results.
Henon *et al*, 1995[113] (full paper)	1986–91	RCo	Grade III	HDT + PBPCT [L-PAM, TBI]	M2 or VAD	22	12	10	75:20 1 year	44:8	–	–	1:0	Control patients had refused BMT, were too old, or were not considered fit enough to receive HDT. It is questionable whether the groups are comparable. Also contains health economics data.
Gianni *et al*, 1994[114] (full paper)	HDT: 1989–91 CC: 1983–86	PH	Newly diagnosed, high labelling index	± VAD HDT + PBPCT [CTX, VCR, MTX, ETOP, L-PAM, TBI]	L-PAM, PRED or alternating VMCP/VBAP	32	13	19	68:25 2 years	41:14	59:4 2 years	38:7	1:0	Pilot study to assess HDT. Controls do poorly.
Cassini *et al*, 1991[115] (abstract)	–	RCo	Adverse prognostic factors	–	–	22	11	11	–	–	63 HDT[b]	–	–	[b] At median follow-up of 19 months. Very little information given. No information, apart from in the title, that survival is improved by HDT. Patients received transplants late. Authors conclude that the QoL is significantly higher in the HDT group.

* *See list of abbreviations of drug names on page ii. EDAP = ETOP, DMS; M2 = BCNU, ELD, CXT, L-PAM; VAD = VCR, ADR, DMS, CYT, CACP.*

QoL = quality of life.

Superscript letters cross-reference to comments column.

continued

TABLE 53 contd *Cohort studies comparing HDT/PCT with CC in multiple myeloma*

Trial reference	Entry years	Study type	Disease eligibility	Treatment regimen* HDT	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Crowley *et al*, 1994[116] (abstract)	–	RCo	Newly diagnosed	HDT + ABMT/ PBPCT + Interferon maintenance	Various	234	101	133	80:60 3 years	–	–	34:12	–	Controls were not well matched: there were major differences in important factors (e.g. age, β-2 microglobulin). HDT as given is very toxic.

* *See list of abbreviations of drug names on page ii. EDAP = ETOP, DMS; M2 = BCNU, ELD, CXT, L-PAM; VAD = VCR, ADR, DMS, CYT, CACP.*

Superscript letters cross-reference to comments column.

TABLE 54 *On-going RCTs in multiple myeloma*

Trial code	Status	Disease eligibility	Treatment regimen* HDT	Treatment regimen* CC	Planned accrual
MRC Myeloma 7	Open	–	ADR, VCR, MPRED, CTX HDT+ ABMT [L-PAM]	ADR, BCNU, CTX, MPRED	750
ECOG	Open	–	HDT + ABMT	–	–

* *See list of abbreviations of drug names on page ii.*

Shaded boxes indicate open UK-based trial.

Chapter 13

Review: breast cancer

Introduction

Breast cancer is the commonest of malignant diseases in women, and in England and Wales there are about 34,000 new cases each year.[117] Thus any benefit of HDT/PCT in breast cancer could have major implications both in terms of public health and NHS resources. Approximately 20,000 patients with metastatic breast cancer undergo HDT/PCT each year in the USA, at an estimated cost of 1 billion dollars.[118]

Patients with advanced disease or metastases, either at diagnosis or following recurrence, are generally considered incurable, although responses to CC are observed in a high proportion of patients, and a small number of long-term survivors are present in some series.[119] To date, the majority of studies of HDT/PCT have focused on metastatic disease in an attempt to establish whether such treatment is potentially effective. High response rates have been demonstrated in several series, but the duration of responses is generally short.

In most cases early breast cancer is treated locally by a combination of surgery and radiotherapy. Adjuvant chemotherapy produces modest improvements in survival for patients.[120] However the prognosis for women with extensive axillary node involvement remains poor and it is in this group of early breast cancer patients that dose intensification and HDT/PCT is now being tested.

Methods

The methods set out in chapter 2 were used. As only three RCTs and no CCTs were identified, data from other comparative studies were also tabulated to provide supplementary qualitative information.

Results

RCTs comparing HDT/PCT with CC in breast cancer

Three randomised trials[121–123] including a total of 197 patients were identified (*Table 55*) all of which investigated the use of HDT/PCT in advanced disease. Two trials[122,123] randomised only those women responding to initial chemotherapy, whereas in the remaining trial[121] no initial chemotherapy was given. Two trials were published as full papers,[121,122] one written in Swedish,[122] and one trial was published as an abstract.[123] Across all studies randomisation took place between 1988 and 1995.

Survival

One publication[123] reported a significant benefit of CC, although it is unclear from the abstract whether the *p* value presented is for comparison of median survivals or from the log rank test. Another publication[121] reported a significantly longer median survival on HDT/PCT but did not present any associated statistics or log rank analyses, although calculated ORs for survival of 0.17 (99% CI 0.05–0.53) at 1 year and 0.10 (99% CI 0.03–0.35) at 2 years are conventionally significant. The third publication[122] did not present any information on survival. Therefore survival results could not be combined.

PFS

Only one report[123] presented a statistical comparison of HDT/PCT with CC, which showed a conventionally significant benefit of HDT/PCT. As this was the only trial to report on this end-point, presenting only median PFS, it was not possible to calculate ORs or combine results.

Cohort studies

Data from cohort studies are summarised in *Table 56*.

Discussion

Despite the large numbers of women who have reportedly been treated with HDT/PCT, particularly for metastatic disease, there is little good quality evidence for its efficacy. The limited evidence that is available from randomised trials in metastatic disease is inconsistent. The trial reported by Bezwoda and colleagues[121] favours HDT/PCT, but the results could potentially be confounded by the use of maintenance tamoxifen: more HDT/PCT patients responded to treatment and were therefore offered tamoxifen, whereas fewer CC patients exhibited a response to treatment and consequently fewer received it. In addition, the

conventional treatment arm had an unusually poor outcome by comparison with other series. An abstract[123] on another trial reported a significantly longer PFS for patients who received HDT/PCT, but significantly better survival for patients who received CC, possibly because a proportion of those treated in the CC arm may subsequently have gone on to receive HDT/PCT at the time of recurrence. A third trial[122] stopped early owing to poor accrual and included too few patients and gave too few details to draw useful conclusions.

Consequently, it is not possible to draw firm conclusions from these trials at present. The results of the large studies now underway (*Table 57*) must be awaited before HDT/PCT can be accepted as a routine part of management. The disease is sufficiently common for reliable evidence to be gathered in a short time if these trials are energetically supported. A systematic review of the literature concerning the use of HDT/PCT in the treatment of metastatic breast cancer, which used somewhat different methodology and was conducted in the USA, reached broadly similar conclusions.[124]

There is as yet no evidence from randomised trials concerning HDT/PCT for breast cancer in the adjuvant setting. As this is the largest group of potential HDT/PCT recipients it is of the highest priority that recruitment into those trials now underway (*Table 57*) is encouraged. Without reliable evidence to guide practice it is likely that the use of HDT/PCT would gradually increase in this group of patients who are usually free of co-morbid conditions and thus able to tolerate the therapy well. The unsatisfactory outcome of conventional adjuvant therapy in patients with extensive axillary lymph node involvement is a powerful factor in this, making it all the more necessary to determine the role of HDT/PCT as soon as possible.

TABLE 55 *RCTs comparing HDT/PCT with CC in metastatic breast cancer*

Trial reference	Entry years	Disease eligibility	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Comments
Bezwoda *et al*, 1995[121] (full paper)	1991–93	Metastatic	HDT + ABMT/ PBPCT [CTX (4800), MTOX (70–90), ETOP (5000)] Tamoxifen maintenance for responders	CTX, MTOX, VCR (6–8 cycles) Tamoxifen maintenance for responders	90	45	45	86:47 1 year 44:3 2 years	21:10	–	0.17 (0.05–0.53) 1 year 0.10 (0.03–0.35) 2 years	–	–	–	–	Tamoxifen given to responders. More patients on HDT received tamoxifen and thus the trial is potentially confounded. Poor survival on CC arm. Authors conclude HDT is suitable for selected younger patients but no statistics are presented, and there is no evidence to substantiate this claim. Sealed envelopes used for randomisation.
Ljungman *et al*, 1995[122] (full paper)	1989–94	Stage III/IV, CR/PR following initial chemo-therapy	–	–	9	4	5	–	–	–	–	–	–	–	–	This Swedish paper mentions nine randomised patients, but does not focus on this. Some information on progression is reported, but it is not in a usable format. Randomisation stopped owing to poor accrual.
Peters *et al*, 1996[123] (abstract)	1988–95	Metastatic, CR follow-ing initial chemo-therapy	ADR, FU, MTX (2–4 cycles) HDT + ABMT [CACP (165), CTX (5625), BCNU (600)]	ADR, FU, MTX (2–4 cycles) HDT on relapse	98	–	–	–	23:38[a]	$p = 0.04$[a]	–	–	11:4[a]	$p = 0.008$[a]	–	Early vs. late transplantation. [a] It is unclear whether the values presented are median survivals/DFS and whether p values refer to LRT. Authors conclude that HDT given initially significantly improves PFS but survival appears superior with HDT given at recurrence.

* *See list of abbreviations of drug names on page ii.*

All trials involved in first-line treatment for advanced disease with no previous chemotherapy for advanced disease; no toxic deaths were reported in any of the trials.

Superscript letters cross-reference to comments column.

TABLE 56 *Cohort studies comparing HDT/PCT with CC in breast cancer*

Trial reference	Entry years	Study type	Disease eligibility	Treatment type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	PFS % HDT:CC	Toxic deaths HDT:CC	Comments
Peters *et al*, 1993[125] & 1995[126] (full papers)	HDT: 1987–91		Stage II/III, > 10 involved nodes	Adjuvant									One HDT cohort, three comparisons, two historical controls, one concurrent control.
Comparison 1		PH			CTX,ADR, FU (4 cycles) HDT + ABMT [CTX (5625), CACP (165), BCNU (600)] + RT	CTX, MTX, FU, VCR, PRED ± immunotherapy	189	85	104	78:45 5 years	71:28 5 years	10:–	Two RCTs are now on-going.
Comparison 2		PH			As comparison 1	CTX, MTX, FU, VCR, PRED ,VBL, ADR, TSPA, FLM	201	85	116	78:48 5 years	71:31 5 years	10:–	
Comparison 3		PC			As comparison 1 + tamoxifen maintenance	CTX,ADR, FU + tamoxifen maintenance	110	85	37	78:37 5 years	71:34 5 years	10:–	
Huelskamp *et al*, 1995[127] (abstract)	–	RCo	Stage IIIB	Consolidation 1st remission (80%) Adjuvant (20%)	Induction chemotherapy HDT + ABMT [CXT (6000), TSPA (800)]	Intensive ADR-based protocol	49	25	24	88:75 at median follow-up 45 months	76:58 at median follow-up 45 months	–	

* *See list of abbreviations of drug names on page ii.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

continued

TABLE 56 contd *Cohort studies comparing HDT/PCT with CC in breast cancer*

Trial reference	Entry years	Study type	Disease eligibility	Treatment type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	No. of patients HDT	No. of patients CC	Survival % HDT:CC	PFS % HDT:CC	Toxic deaths HDT:CC	Comments
Gianni *et al*, 1995[128] (abstract)	1988–92	RH	> 10 involved nodes	Adjuvant									One HDT cohort compared with two control cohorts from RCT.
Comparison 1					HDT + PBPCT [CTX, MTX, VCR, CACP, L-PAM + RT]	Sequential ADR/CTX, MTX, FU	125	67	58	78:60 5 years	56:41 5 years	1:–	Subset of patients with 10–15 nodes +ve was also analysed.
Comparison 2					As comparison 1	Alternating ADR/CTX, MTX, FU	135	67	68	78:60 5 years	56:33 5 years	1:–	A randomised trial is on-going.

* *See list of abbreviations of drug names on page ii.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 57 *On-going RCTs and RCTs not yet reported in breast cancer*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
CLB-9082† INT-0163	Open	Stage IIA, IIB, IIIA Includes QoL assessments	CTX, ADR, FU HDT + ABMT/PBPCT [CTX, CACP, BCNU]	CTX, ADR, FU CTX, CACP, BCNU	800
EST-2190† INT-0121	Open	Stage II/III epithelial	CTX, ADR, FU HDT + ABMT/PBPCT [CTX, TSPA]	CTX, ADR, FU –	534
Anglo Celtic Study EU-95048†	Open	High-risk disease Stage II or IIIA	HDT + PBPCT [CTX, TSPA]	CTX, MTX, FU	450
SWOG-S9623 SWOG-9623	Open	Primary	HDT + ABMT/PBPCT [CTX, CACP, BCNU or CTX, CBDSA, TSPA]	Intensive sequential chemotherapy [ADR, TAX, CTX]	1000
Dutch Working Party for ABMT in solid tumours[129]	Open	Adjuvant treatment Includes cost-effectiveness study	FU, EPI, CTX HDT + ABMT [CTX, TSPA, CBDSA]	FU, EPI, CTX –	?
Stockholm Breast Cancer Study Group[130]	Open	High risk Adjuvant	FU, EPI, CTX HDT + ABMT [CTX, THIO, CBDSA]	FU, EPI, CTX –	200
Instituto Nazionale Tumori, Milan[128]	Open?	Adjuvant	HDT + PBPCT [includes EPI, L-PAM]	Sequential ADR, CTX, FU, MTX	?
PEGASE 01 EBMT Trial	Open	≥ 8 positive nodes	FU, EPI, CTX HDT + ABMT [CTX, MTX, L-PAM]	FU, EPI, CTX –	> 150

* *See list of abbreviations of drug names on page ii.*

† *PDQ trial reference code.*

Shaded boxes indicate open UK-based and EBMT trials.

continued

TABLE 57 contd *On-going RCTs and RCTs not yet reported in breast cancer*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
E-PBT01 NCI-T90-0180D	Open	Metastatic	HDT + PBPCT/ABMT [CTX, TSPA, CBDSA]	CTX, MTX, FU	549
PEGASE 03 EBMT Trial	Open	Metastatic	FU, EPI, CTX HDT + ABMT [CTX, TSPA + CBDSA]	FU, EPI, CTX –	> 130
NCI-84-C-216† NCI-T84-0518N NCI-86-C-188 NCI-MB-198	Closed 05/02/97	Stage III/IV	CTX, ADR, MTX, FU, TMX HDT + ABMT [L-PAM] + Maintenance therapy	CTX, ADR, MTX, FU, TMX – + Maintenance therapy	200
SLUMC-6149† NCI-V91-0151	Closed 23/08/93	Metastatic High-risk primary	HDT + ABMT/PBPCT [CACP, CTX, ETOP]	5-FU, ADR, CTX ± mastectomy	44–128
SLUMC-7276† NCI-V93-0307	Closed 11/05/94	Metastatic High-risk primary stage II/III	FU, ADR, CTX HDT + ABMT/PBPCT [CTX, ETOP, CACP, CBDSA, TXL]	–	44–128
SWOG-9115† INT-0127	Closed 01/01/94	Recurrent or metastatic	HDT + ABMT/PBPCT [CTX, TSPA, CBDSA] Anti-oestrogen therapy	Standard chemotherapy regimen Anti-oestrogen therapy	300
Maximum planned accrual ...					**> 4569**

* *See list of abbreviations of drug names on page ii.*

† *PDQ trial reference code.*

Shaded boxes indicate open UK-based and EBMT trials.

Chapter 14

Review: germ-cell tumours

Introduction

Non-seminomatous germ-cell tumours provide a model for chemotherapy-curable malignancies. With the use of platinum-containing combination treatment, and where necessary follow-up surgery, approximately 80% of patients with metastatic disease may expect cure.[131] However, for the few men in whom initial treatment fails to produce a complete remission, or the small proportion of patients in which the disease recurs, the outlook is much less satisfactory. Conventional 'salvage' regimens may cure around a third of such patients[132] but for the majority the illness proves fatal. The testing of high-dose chemotherapy with autologous stem cell rescue is a logical response to the frequent failure of 'salvage' therapy, given the demonstrable chemo-sensitivity of most cases.

High-dose treatments have principally been applied following recurrence after conventional treatment. More recently, the identification of prognostic features at the time of presentation has allowed the description of a high-risk subgroup in which the results of conventional therapy are less satisfactory (41% PFS at 5 years[131]) and for which elective intensification may be appropriate as a part of initial treatment.

Methods

The methods set out in chapter 2 were used. Only one RCT and no CCTs were identified and so data from the one relevant comparative study were also tabulated to provide supplementary qualitative information.

Results

RCT comparing HDT/PCT with CC in germ-cell tumours

One randomised trial[133] including a total of 114 patients with poor-prognosis metastatic non-seminomatous germ-cell tumours was identified (*Table 58*). Randomisation took place between 1988 and 1991 and the trial was reported as a full paper in 1993.

Survival

No evidence of a difference in overall survival between high-dose and conventional therapy was reported.

PFS

PFS at a median follow-up of 24 months was reported to favour CC, but no statistics were presented for this end-point. No curve was presented and the percentage alive and free from progression was not given. Therefore it was not possible to calculate ORs.

Cohort studies

Data from cohort studies are summarised in *Table 59*.

Discussion

Only one randomised trial has addressed the use of HDT/PCT in therapy for germ-cell tumours. This trial of patients with poor-prognosis metastatic tumours found no evidence that HDT/PCT is more effective in this situation, although with only 114 patients randomised only large differences in efficacy would have been reliably detected. In addition there were several potential confounding factors in the design of the trial: in particular, the planned dose of the most active agent, cisplatin, was identical in both the HDT/PCT and the CC regimens. Accordingly, no conclusion can be drawn regarding the efficacy of HDT/PCT in this setting.

The unsatisfactory results of CC in poor-prognosis patients often leads some clinicians to use HDT/PCT in the treatment of germ-cell tumours, particularly following recurrence, but there remains no clear evidence on which to base such practice. Those trials currently in progress (*Table 60*) should provide evidence of the efficacy of HDT/PCT both following recurrence and as part of initial therapy for those with poor prognostic features. However, owing to the low incidence of these tumours, such trials will require national and international collaboration to achieve adequate statistical power.

TABLE 58 *RCT comparing HDT/PCT with CC in germ-cell tumours*

Trial reference	Entry years	Disease eligibility	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	Toxic deaths HDT:CC	Comments
Chevreau *et al*, 1993[133] (full paper)	1988–91	Poor prognosis, metastatic NSGCT	VBL, ETOP, BLM, CACP (2 cycles) HDT + ABMT [CACP (200), ETOP (1750), CTX (6400)]	VBL, ETOP, BLM, CACP (3–4 cycles)	57	57	60:80 2 years	$p = 0.08$	2.71 (0.95–7.76) 2 years	58:70[a]	–	–	2:3	One patient excluded (paper does not state from which arm). The total dose of CACP was the same in the HDT and CC arms of the study. [a] At median follow-up at 24 months. Authors conclude that the trial provides no evidence that HDT is effective.

* *See list of abbreviations of drug names on page ii.*
NSGCT = non-seminomatous germ-cell tumour.
Superscript letters cross-reference to comments column.

TABLE 59 *Cohort studies comparing HDT/PCT with CC in germ-cell tumours*

Trial reference	Entry years	Disease eligibility	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients HDT	No. of patients CC	Survival % HDT:CC	PFS % HDT:CC	Comments
Bokemeyer *et al*, 1995[134] (abstract)	HDT: 1989–94	Poor prognosis by IGCCCG criteria	RH	HDT + PBPCT [Dose escalated to: CACP, 600; ETOP, 5000; IFOS, 4000; (+ GCSF or GMCSF)]	–	83	–	72:55 2 years	68:50 2 years	Compared with test set of patients used to develop IGCCCG model. HDT escalated up to given doses; 45/118 patients received levels 3–5.

* *See list of abbreviations of drug names on page ii.*
GCSF = granulocyte colony stimulating factor; GMCSF = granulocyte-macrophage colony stimulating factor; IGCCCG = International Germ Cell Cancer Collaborative Group.
The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 60 *On-going RCTs and RCTs not yet reported in germ-cell tumours*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
FRE-FNCLCC-IT94† NCI-F94-0019	Open	Testicular or extragonadal male germ-cell tumours	CACP, ETOP, IFOS or VBL, IFOS, CACP HDT + ABMT/PBPCT [CBDSA, ETOP, CTX]	CACP, ETOP, IFOS or VBL, IFOS, CACP –	220
MSKCC-94076† NCI-T94-0086D	Open	Poor- and intermediate-risk male NSGCT	BLM, ETOP, CACP HDT+ ABMT/PBPCT [CBDSA, ETOP, CTX]	BLM, ETOP, CACP –	218
NCI-81-C-123† NCI-N82-526 NCI-MB-155	Closed 15/12/86	Poor prognosis testicular carcinoma	CACP, VBL, BLM, ETOP ± surgery HDT+ ABMT [CACP, ETOP]	CACP, VBL, BLM ± surgery –	51
Maximum planned accrual ...					**489**

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*

Chapter 15

Review: small cell lung cancer

Introduction

Lung cancer is the leading cause of cancer-related deaths and worldwide more than half a million new cases are diagnosed annually.[135] About 20% of lung cancers are of the small cell histological type,[136] and the majority of patients present with extensive disease. Small cell lung cancer (SCLC) has been shown to be sensitive to cytotoxic agents, but only about 5% of patients survive for more than 2 years.[137] In an attempt to improve survival rates, dose intensification supported by autologous transplantation has been investigated in patients responding to induction chemotherapy. Non-SCLC is less sensitive to chemotherapy, and as far as it is known no studies have been performed to investigate HDT/PCT in this disease.

Methods

The methods set out in chapter 2 were used. As only one RCT and no CCTs were identified, data from the one relevant comparative study that was found were also tabulated to provide supplementary qualitative information.

Results

RCT comparing HDT/PCT with CC in SCLC

One randomised trial[138] including a total of 45 patients with limited stage SCLC who were in complete or partial remission following induction chemotherapy was identified (*Table 61*). Randomisation took place between 1980 and 1985 and the trial was reported as a full paper in 1987.

Survival

No evidence of a difference in overall survival was reported.

PFS

A conventionally significant benefit in PFS with HDT/PCT was reported.

Cohort study

Data from a cohort study are summarised in *Table 62*.

Discussion

Only one trial investigating HDT/PCT in SCLC was identified. This trial reported a significant increase in PFS for the HDT/PCT arm with no evidence of a survival benefit. However, owing to the small number of patients randomised only large differences in efficacy could have been detected reliably and the results must therefore be interpreted cautiously. The authors also comment that it was not clear whether progenitor cell support was necessary for the administration of the 'high-dose chemotherapy' given in the trial. Accordingly, no conclusion can be drawn regarding the role of HDT/PCT in this setting.

Investigation of HDT/PCT in SCLC has been restricted by the co-morbidity in the relatively elderly patient population, which makes many candidates unsuitable for intensive chemotherapy regimens, and there is a perception that HDT/PCT is ineffective. This perception is, however, not based upon reliable evidence, as the findings of this review make clear. Further randomised studies involving patients fit enough to tolerate such treatment are justified, but it should be noted that this approach will only be appropriate in the minority of cases. Despite the unsatisfactory results of CC, HDT/PCT cannot be regarded as a routine part of management and participation in on-going trials (*Table 63*) should be encouraged.

TABLE 61 *RCT of HDT/PCT versus CC in SCLC*

Trial reference	Entry years	Disease eligibility	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients Total	HDT	CC	Survival % HDT:CC	Survival Median (months) HDT:CC	Survival Statistics in paper	Survival Calculated OR (99% CI)	PFS % HDT:CC	PFS Median (months) HDT:CC	PFS Statistics in paper	PFS Calculated OR (99% CI)	Toxic deaths HDT:CC	Comments
Humblet *et al*, 1987[138] (full paper)	1980–85	CR/PR after induction chemo-therapy and PCI	MTX, VCR, CTX, ADR (3 cycles) CACP, ETOP (2 cycles) + PCI HDT + ABMT [CTX (6000), ETOP (500), BCNU (300)]	MTX, VCR, CTX, ADR (3 cycles) CACP, ETOP (2 cycles) + PCI CTX, ETOP, BCNU	45	23	22	61:54 1 year 30:9 2 years	17:14	$\chi^2 = 2.31$ $p = 0.13$	0.78 (0.17–3.62) 1 year 0.27 (0.04–1.82) 2 years	23:0 1 year 13:0 2 years	7:2.5	$\chi^2 = 9.8$ $p = 0.002$	0.12 (0.01–1.31) 1 year 0.13 (0.01–2.72) 2 years	4:0	Survival measured from first day of induction but PFS measured from randomisation. Authors state that it is not clear that ABMT was necessary for HDT. Authors conclude that HDT did not result in significant improvements in overall survival. There was an improvement in PFS. The authors suggest that HDT deserves further investigation. Sealed envelopes used for randomisation.

* *See list of abbreviations of drug names on page ii.*

PCI = prophylactic cranial irradiation

TABLE 62 *Cohort studies comparing HDT/PCT with CC in SCLC*

Trial reference	Entry years	Disease eligibility	Study type	Treatment regimen* HDT (total dose, mg/m^2)	Treatment regimen* CC	No. of patients HDT	No. of patients CC	Survival % HDT:CC	Survival Median (months) HDT:CC	PFS % HDT:CC	PFS Median (months) HDT:CC	Toxic deaths HDT:CC	Comments
Souhami *et al*, 1989[139] (full paper)	1980–?			HDT + ABMT	CTX, VCR, ETOP								
Comparison 1		SCLC, –ve BM, limited disease	PC	[CTX (160–200 mg/kg)]		25	–	67:47 1 year 33:15 2 years	18.5:11	–	8.5:–	0:–	Four HDT regimens were compared with a control population with matching prognostic factors taken from an RCT.
Comparison 2		SCLC, –ve BM, limited disease	PC	[CTX (320–400), ETOP (800–1200 mg/kg)]		26	–	48:47 1 year 12:15 2 years	11:11	–	10:–	3:–	
Comparison 3		SCLC, –ve BM, limited disease	PC	[ADR (100), ETOP (720), VCR (4), CTX (200)]		15	–	33:47 1 year 13:15 2 years	11:11	–	7.5:–	2:–	
Comparison 4		SCLC, –ve BM, limited disease	PC	[Either: CBDS (400–600), ETOP (480) or L-PAM (140), CTX (160 mg/kg)]		9	–	51:47 1 year 33:15 1.5 years	14:11	–	8:–	0:–	

* *See list of abbreviations of drug names on page ii; total dose mg/m^2 unless otherwise stated.*

The studies reported in this table are not randomised trials, and therefore the results should be viewed in the light of the problems and biases associated with non-randomised comparisons.

TABLE 63 *On-going RCTs and RCTs not yet reported in SCLC*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
EBMT	Open	Localised or extensive disease	EPI, TXL HDT + ABMT [high-dose IFOS, CBDSA, ETOP]	 Standard dose IFOS, CBDSA, ETOP	400
MDA-DT-7738†	Closed 09/01/80	Localised or metastatic oat cell carcinoma of the lung	HDT + ABMT [VCR, CTX, ETOP, BCNU]	VCR, CTX, ETOP, BCNU	–
MDA-DT-8065† NCI-D81-043-347	Closed 04/01/84	Limited SCLC	ETOP, CTX, ADR, VCR, curative surgery HDT + ABMT [CTX, ETOP, MTX ± RT] ETOP, CTX, ADR, VCR	ETOP, CTX, ADR, VCR, curative surgery ETOP, CTX, ADR, VCR MTX ± RT ETOP, CTX, ADR, VCR	120
Maximum planned accrual ...					**520+**

* *See list of abbreviations of drug names on page ii.*
† *PDQ trial reference code.*

Shaded boxes indicate open EBMT trials.

Chapter 16

Review: ovarian cancer

Introduction

Ovarian cancer is generally asymptomatic in the early stages. Consequently, the majority of women present with advanced disease and tumour spread to the peritoneal cavity and beyond. Cytoreductive surgery is usually followed by chemotherapy. A recent systematic meta-analysis of individual patient data has suggested that platinum-based regimens are more effective than non-platinum regimens and that cisplatin and carboplatin are equally effective.[140,141] Much recent research has focused on the taxanes for which the majority of RCTs are expected to report in the near future. Intensification of treatment (without transplantation) has been tested to determine whether the number of long-term remissions may be increased in advanced disease and recent Phase II studies of HDT with autologous support have reported promising results, although no randomised trials have yet been reported.[142]

Methods

The methods set out in chapter 2 were used.

Results

No trial nor comparative study of HDT/PCT versus CC in ovarian cancer was identified.

Discussion

At present there is no reliable evidence concerning the use of HDT/PCT in ovarian cancer. However, two RCTs are in progress and a further trial coordinated by the EBMT has been launched (*Table 64*). The use of HDT/PCT in the treatment of ovarian cancer should still be considered an experimental treatment the efficacy of which must be assessed in RCTs, and recruitment into these trials should be encouraged.

TABLE 64 *On-going RCTs and RCTs not yet reported in ovarian cancer*

Trial code	Status	Disease eligibility	Treatment regimen*		Planned accrual
			HDT	CC	
GOG-164	Open	Low-volume ovarian epithelial carcinoma	HDT + ABMT/PBPCT [CBDCA, CTX, MITX]	TXL, CBDCA	275
GINECO	Open	Minimal or no residual disease	HDT + PBPCT [CBDSA, CTX]	CBDSA, CTX	–
EBMT; Study coordinator J Lederman	Open	FIGO stage III/IV, < 2 cm residual disease	HDT + ABMT [CTX,TXL, CBDSA, L-PAM]	CBDSA or CDDP + TXL	300
Maximum patient accrual ...					**> 575**

* *See list of abbreviations of drug names on page ii.*

Shaded boxes indicate open EBMT trials.

Chapter 17

Health economics review

Introduction

HDT/PCT is readily identified as a procedure of considerable cost, arising from the expense of prolonged hospital care, high-technology medical interventions and the provision of specialised facilities. However, the true cost of HDT/PCT must be considered in relation to both the long-term consequences and the cost of administering CC to similar patient populations (*Table 65*).

Methods

The search strategies described in chapter 2 were used to identify relevant health economics studies.

The conclusions of cost-effectiveness analyses based on the results of cohort studies are subject to the same potential biases in the assessment of effectiveness as those previously described for similar comparisons of clinical data and are consequently unreliable.[4] Therefore, for those studies that reported cost-effectiveness ratios based on data from sources other than RCTs or CCTs, only cost data are presented.

The cost data presented have, where possible, been converted to the equivalent cost in 1993 US dollars using purchasing power parities published by the OECD in August 1997 and the US *All Goods Consumer Price Index* published by the Bureau of Labor Statistics. Where the paper did not present the year for which the prices were calculated, an estimation was made based on the year of publication and the years in which patients were recruited.

TABLE 65 *Comparison of cost factors in the initial treatment for PCT and CC*

Procedure	PCT	CC
Set-up	Setting up a specialist bone-marrow transplantation unit is expensive. However this is a single expenditure.	CC utilises the same facilities as chemotherapy for other malignancies.
Hospitalisation	Hospitalisation may not be necessary for peripheral blood progenitor cell harvesting, but is required for bone-marrow harvesting. It is usually necessary after HDT and may include time in an isolation room or intensive care.	For some malignancies CC will be given on an outpatient basis and hospitalisation will occur only for adverse events. For other malignancies CC is intensive and hospitalisation is required.
Outpatient visits	Follow-up visits are necessary on completion of treatment.	Some CC will be given on an outpatient basis. Follow-up visits are necessary after completion of outpatient or inpatient treatment.
Laboratory costs	Laboratory costs are relatively high because of the need to process the progenitor cells and the number of routine blood tests required.	Routine tests only are necessary.
Drugs and nutritional costs	Drugs and parenteral nutrition are needed.	There are costs for drugs, but parenteral nutrition is not needed. Drugs may be administered over a longer period of time
Radiotherapy	TBI is common.	Targeted radiotherapy is more common
Transfusions	Transfusions are often necessary because of myelotoxicity.	Transfusions are not usually necessary except in an emergency.
Procedural costs	The cost of bone-marrow harvest must be included.	–

Results

Fifteen studies comparing the cost and/or the cost-effectiveness of HDT/PCT with those of conventional therapy were identified (*Tables 66* and *67*). All used bone marrow as a source of progenitor cells. In the ten studies which looked at the cost of HDT/PCT in leukaemia, all costed allogeneic transplantation and two studies[143,144] also costed autologous transplantation. In all other disease sites, the cost of autologous transplantation was addressed. Across all studies the patients were treated between 1973 and 1993.

Fourteen studies comparing the cost and/or the cost-effectiveness of BMT versus those of PBPCT in a variety of malignancies were also identified (*Tables 68* and *69*). Across all studies the patients were treated between 1988 and 1995.

HDT/PCT versus CC

Only four of the identified studies[143,145–147] used the results of RCTs or CCTs as efficacy measures. Although these reports derived cost-efficacy figures based upon observed differences in outcome between HDT/PCT and CC, as would be expected given their small size none showed therapeutic results that reached conventional levels of significance. If efficacy cannot be considered significantly different, then the only changing variable in a cost-effectiveness analysis will be cost. Therefore, although the results of cost-effectiveness analyses are tabulated, only cost data are considered further.

All but two analyses[144,148] conducted on treatment of leukaemia concluded that HDT/PCT was more expensive than CC. The cost of administering BMT and some subsequent therapy in acute leukaemia (first and second remission, autologous and allogeneic transplantation) was reported to be around 1–2 times the cost of CC in all studies[143–146,148–152] except one[153] (in which BMT was reported to be five times the cost of CC). In other diseases the cost of BMT was found to be between 1 and 5 times the cost of conventional therapy.[147,154–156]

All analyses were based on the mean costs from small patient cohorts, the majority of which were not from randomised or pseudo-randomised trials. It is therefore possible that these data are not representative of the cost of either treatment modality.

PBPCT versus BMT

Thirteen comparative studies were identified in which the costs of administering HDT/BMT were compared with those of treatment with HDT/PBPCT (*Tables 68* and *69*). All but two[157,158] studies were known to be carried out retrospectively. The average cost of a BMT was reported to be 1–1.7 times that of a PBPCT.

Discussion

HDT/PCT versus CC

The cost-effectiveness of HDT/PCT has yet to be reliably determined, largely because the true efficacy of HDT/PCT compared with CC is unproven. Even in those studies that used the results of RCTs or CCTs, sample sizes were small and unable reliably to detect moderate differences in outcomes. As with any therapy the cost-effectiveness of HDT/PCT is likely to vary depending upon the condition being treated. In most cases, HDT/PCT is given with curative intent and therefore differences in efficacy of HDT/PCT and CC will influence the cost-effectiveness ratio. In some conditions, for example childhood ALL, the main potential advantage of HDT with autologous transplantation may be to decrease overall treatment time even if little gain in long-term survival is expected. The timing of HDT/PCT may also affect the cost-effectiveness of treatment. For example, HDTPCT may be used either early in treatment or following first or second relapse. If HDT/PCT prevents many more relapses than CC, it may be more cost-effective to use HDT/PCT as part of initial therapy. If, however, HDT/PCT prevents only a few relapses, it may be more cost-effective to reserve this approach for patients with recurrences. These issues highlight the need for more prospective quality of life studies to assess the benefits to patients of different treatment approaches.

A further aspect of HDT/PCT which has still to be fully addressed and which will greatly influence estimates of cost/cost-effectiveness is that of long-term toxicity. Reliable evidence of the comparative incidences of serious long-term toxicities (such as second malignancies) in patients treated with CC and HDT/PCT is unavailable and will come only from the maturation of RCTs and CCTs (see chapter 19). If HDT/PCT causes a greater number of late side-effects than CC, then the overall costs of HDT/PCT will increase and the survival rate will decrease. The economic consequences of long-term toxicities will be most apparent in those diseases for which the patients have the greatest survival times.

At present there is insufficient evidence to comment on the cost-effectiveness of HDT/PCT compared with CC in any malignancy because of

the lack of reliable evidence of the comparative efficacy of the two treatments. Further prospective cost-effectiveness studies are required which utilise the results of large reliable RCTs as measures of the comparative clinical outcome of HDT/PCT and CC. Ideally the efficacy measure would be taken from the results of a meta-analysis of individual patient data.

PBPCT versus BMT

In most studies PBPCT was reported to cost less than BMT. The authors generally conclude that the differences in the cost of the two procedures were due mainly to the faster haematological recovery with PBPCT. This reduces the time that a patient is at risk from infection, which in turn decreases hospitalisation (especially in intensive care), and is likely to reduce the numbers of transfusions and routine laboratory tests performed.

Several small randomised comparisons of BMT versus PBPCT have been performed (see chapter 18). The results of three out of four of these RCTs confirm the findings of the cohort studies, in that PBPCT decreases haematological recovery time with no difference in long-term survival and/or PFS. If the results of these small RCTs are confirmed in larger studies, it could be concluded that the introduction of PBPCT in place of BMT would reduce the cost of HDT/PCT.

TABLE 66 *Economic comparisons of HDT/BMT with CC using the results of RCTs or CCTs as efficacy measures*

Reference	Entry years	Type of BMT	Type of evaluation	Costs included[†]	Method for determining total resources used	No. of patients	Patients from RCT/CCT	Outcomes: Cost[‡]	Outcomes: CEA/CUA[§]	Outcomes: Cost as 1993 US$	Details of sensitivity analysis	Comments
AML: consolidation of first CR												
Welch & Larson, 1989[145] (full paper)	1978–82	AlBMT	CEA	**	Retrospective Global cost model over 5 years	41	Genetic selection	(1989) First 5 years: BMT: US$193,000 CC: US$136,000 First 6 months: BMT: US$139,000 CC: US$78,000	Marginal cost for BMT: US$59,300/LYS	First 5 years: BMT: $224,907 CC: $158,483 First 6 months: BMT: $161,979 CC: $90,895	Results insensitive to varying the discount rate. If the gain in survival was > 40% then the cost-effectiveness was similar to/better than that of chemotherapy.	US$10,000/LYS if 30-year tail used. ITU use was found to be the biggest difference in cost. Only 5% of hospital days were in the ITU for patients receiving CC, compared with 57% of time for the HDT group.
Corker, 1989[146] (abstract)	–	AlBMT	CEA	?	Retrospective Actual usage	–	Genetic selection	–	Marginal cost for BMT: US$70,000/LYS[a]	–	–	No clinical benefit for BMT in first 4 years compared with intensive consolidation, but benefit in comparison with less intensive consolidation. [a] It is unclear to which chemotherapy regimen this refers. Author notes that adjustments for age and QoL remove any advantage to BMT.

[†] *Cost ratings: * = procedure costs only; ** = procedure + subsequent therapy; *** = procedure + subsequent therapy + set-up costs.*

[‡] *Date of assessment in brackets if available.*

[§] *Date as for cost column.*

Superscript letters cross-reference to comments column.

CEA = cost-effectiveness analysis; CUA = cost utility analysis; ITU = intensive treatment unit; LYS = life-years saved; QALY = quality of life years saved.

continued

TABLE 66 contd *Economic comparisons of HDT/BMT with CC using the results of RCTs or CCTs as efficacy measures*

Reference	Entry years	Type of BMT	Type of evaluation	Costs included[†]	Method for determining total resources used	No. of patients	Patients from RCT/CCT	Outcomes: Cost[‡]	Outcomes: CEA/ CUA[§]	Outcomes: Cost as 1993 US$	Details of sensitivity analysis	Comments
***AML: consolidation of first CR* contd**												
Dufoir *et al*, 1992[143] (full paper)	1984–89	AlBMT/ ABMT	Costing	***	Retrospective Actual usage	40	ABMT vs. chemotherapy, RCT AlBMT vs. chemotherapy, genetic allocation	(1991) AlBMT: FF 424,696 ABMT: FF 505,364 CC: FF 304,846	–	AlBMT: $68,269 ABMT: $81,237 CC: $49,004	Cost analysis with and without costs of relapse therapy. Costs were significantly higher for both AlBMT and ABMT groups, regardless of whether relapse therapy was included.	Four of the ABMT patients underwent double grafting. Authors conclude that AlBMT is the best therapeutic and economic approach.
NHL												
Uyl-de Groot *et al*, 1995[147] (full paper)	1987–93	ABMT	CEA	**	Retrospective Actual usage/ model	42	RCT	(1992) BMT: US$49,983 CC: US$15,285	Markov model predictions: BMT: US$11,132/LYS, US$13,016/QALY CC: US$3032/LYS, US$3530/QALY	BMT: $51,479 CC: $15,742	–	BMT is more expensive and did not improve survival. Dutch study. Costs and QALYs discounted at 5%. Costs from a randomised trial taken for the first 2 years; then costs calculated from a Markov model.

[†] *Cost ratings: * = procedure costs only; ** = procedure + subsequent therapy; *** = procedure + subsequent therapy + set-up costs.*

[‡] *Date of assessment in brackets if available.*

[§] *Date as for cost column.*

Superscript letters cross-reference to comments column.

CEA = cost-effectiveness analysis; CUA = cost utility analysis; ITU = intensive treatment unit; LYS = life-years saved; QALY = quality of life years saved.

TABLE 67 *Economic comparisons of HDT/BMT vs. CC using the results of non-RCTs/CCTs as efficacy measures*

Reference	Entry years	Type of BMT	Type of evaluation	Costs included†	Method for determining total resources used	No. of patients	Outcomes: Cost‡	Outcomes: Cost as 1993 US$	Details of sensitivity analysis	Comments
AML: consolidation of first remission										
Masoka, 1994[149] (abstract)	1985–87	AlBMT	CEA	**	Retrospective Actual usage calculated from bill to government insurance	38	BMT: ¥17,942,131 CC: ¥13,495,527	BMT: $97,512 CC: $73,345	–	Authors suggest that BMT is an economical treatment compared with therapies such as dialysis. Japanese patients treated.
Viens-Bitker *et al*, 1986[150] (full paper)	–	AlBMT	Costing	*	Models	–	(1984) BMT: FF 241,351 BMT + GVHD: FF 328,742 CC: FF 131,537	No PPP data available for this year	–	Cost-modelling analysis only. Paper is in French. Costs are calculated for transplants with and without GVHD complications.
Armitage *et al*, 1984[153] (full paper)	1973–81	AlBMT	Costing	**	Retrospective Actual usage	33	(1981) BMT: US$84,102 CC: US$16,801	BMT: $133,634 CC: $26,707	–	Authors comment that AlBMT is more expensive, more toxic and results in poorer survival than CC in the first year. Follow-up on the patients is short.
Aulesa *et al*, 1992[144] (full paper)	–	AlBMT/ ABMT	Costing	**	Retrospective Actual usage	4	(1991) AlBMT: Pts 10,958,954 ABMT: Pts 14,399,731 CC: Pts 11,740,190	AlBMT: $103,811 ABMT: $136,404 CC: $111,211	–	Paper is in Spanish.

† *Cost ratings: * = procedure costs only; ** = procedure + subsequent therapy; *** = procedure + subsequent therapy + set-up costs.*

‡ *Date of assessment in brackets if available.*

Superscript letters cross-reference to comments column.

PPP = purchasing power parities

continued

TABLE 67 contd *Economic comparisons of HDT/BMT vs. CC using the results of non-RCTs/CCTs as efficacy measures*

Reference	Entry years	Type of BMT	Type of evaluation	Costs included†	Method for determining total resources used	No. of patients	Outcomes: Cost‡	Outcomes: Cost as 1993 US$	Details of sensitivity analysis	Comments
AML: consolidation of second CR										
Barr *et al*, 1996[148] (full paper)	1986–90	AlBMT	CEA/CUA	***	Retrospective Actual usage	7	(1992) BMT: Can$100,600 CC: Can$51,800	BMT: $81,584 CC: $42,008	Results not sensitive to a variety of factors, including time horizons, discounting LYG and duration of hospital stay	5% discount on life-years, but not on costs.
ALL: consolidation of first CR										
Barr *et al*, 1996[148] (full paper)	1986–90	AlBMT	CEA/CUA	***	Retrospective Actual usage	11	(1992) BMT: Can$92,000 CC: Can$102,800	BMT: $74,610 CC: $83,368	Results sensitive to the duration of hospitalisation.	Authors note that CC is expensive.
AML and ALL: evaluation combined										
Rollinson, 1982[151] (full paper)	1975–81	AlBMT[a]	Costing	**	Retrospective Actual usage	2 BMT 16 CC	(1981) BMT: NZ$11,979 CC: NZ$7279	No PPP data available for this year	–	12 AML, 7 ALL. [a] AML and ALL considered together. No indication as to disease status of patients.
Kay *et al*, 1980[152] (full paper)	–	AlBMT	Costing	**	Retrospective Actual usage for BMT procedure, other quantities estimated	22 (BMT)	(1978/1979) BMT: £11,564 CC: £7500	No PPP data available for this year	–	Costs of conventional treatment were estimated. Authors assume that all chemotherapy patients and only 1/4 of BMT recipients will relapse. Authors note that the NHS price index rose by 25.4% from time of writing to time of publication.

† *Cost ratings: * = procedure costs only; ** = procedure + subsequent therapy; *** = procedure + subsequent therapy + set-up costs.*
‡ *Date of assessment in brackets if available.*
Superscript letters cross-reference to comments column.
PPP = purchasing power parities

continued

TABLE 67 contd *Economic comparisons of HDT/BMT vs. CC using the results of non-RCTs/CCTs as efficacy measures*

Reference	Entry years	Type of BMT	Type of evaluation	Costs included[†]	Method for determining total resources used	No. of patients	Outcomes		Details of sensitivity analysis	Comments
							Cost[‡]	Cost as 1993 US$		
Myeloma: first-line therapy										
Henon *et al*, 1995[159] (full paper)	1986–91	ABMT	CUA	**	Retrospective Cox Model	22	(1993) BMT: US$56,700 CC: US$46,555	BMT: $56,700 CC: $46,555	–	Patients were treated in France. Differences in cost were largely attributable to use of ITU.
NHL: consolidation of first PR										
Zaidi *et al*, 1996[154] (abstract)	–	ABMT	CEA	*	–	11	BMT: US$27,000 (£18,000) CC: US$6000 (£4000)	BMT: $25,473 CC: $5660	–	Little information supplied. UK study.
Hodgkin's disease: treatment of recurrent disease										
Desch *et al*, 1992[155] (full paper)	1980–91	ABMT	CEA	**	Retrospective Model	–	BMT: US$76,500[b] CC: US$16,300	BMT: $84,577 CC: $18,021	–	Analysis modelled BMT usage in various disease status following recurrence. [b] Cost for what was considered to be the optimum BMT strategy (BMT in second relapse). Other costs ranged from US$74,000 to US$110,100.
Metastatic breast cancer										
Hillner *et al*, 1992[156] (full paper)	1990–91	ABMT	CEA	**	Markov model	–	(1990) BMT: US$89,700 CC: US$36,100	BMT: $99,171 CC: $39,911	–	5% discounting of costs and benefits. 30-year survival tail reduced costs by 75%. Clinical outcome measures were derived from the literature.

[†] *Cost ratings: * = procedure costs only; ** = procedure + subsequent therapy; *** = procedure + subsequent therapy + set-up costs.*

[‡] *Date of assessment in brackets if available.*

Superscript letters cross-reference to comments column.

TABLE 68 *Comparisons of the cost of time to engraftment for BMT vs. PBPCT for studies using the results of RCTs as efficacy measures*

Reference	Entry years	Disease	Type of evaluation	Costs included[†]	Method for determining total resources used	End-points	No. of patients	Outcomes: Cost[‡]	Outcomes: Cost as 1993 US$	Details of sensitivity analysis	Comments
Le Corroller *et al*, 1997[157] (full paper)	1993–94	Various	Costing Cost-effectiveness	*	Prospective actual usage	TTE	129	(1995) Adults: BMT: FF 156,358 PBPCT: FF 129,751 Children: BMT: FF 181,972 PBPCT: FF 129,458	Adults BMT: $22,395 PBPCT: $18,583 Children: BMT: $26,063 PBPCT: $18,542	Daily room cost, drug price and laboratory test prices were investigated. In all cases PBPCT remained the cheapest option.	Patients treated in France. 48 paediatric patients, 81 adult patients. Time to engraftment was shorter with PBPCT than with BMT. Efficacy data taken from a multicentre trial[160] (see *Table 70*). Authors conclude that costs are significantly lower with PBPCT than with BMT in both childen and adults.
Smith *et al*, 1997[158] (full paper)	–	HD and NHL recurrent	Costing	*	Prospective assessment of actual usage	TTE	58	(1995) BMT: US$59,314 PBPCT: US$45,792	BMT: $56.239 PBPCT: $43,418	Looked at making the cost of PBPC collection equivalent to BMT, the cost of treating patients with no ITU care and reducing the cost of the drugs. In all cases PBPCT was about 20% cheaper.	Authors comment that shorter time in hospital for PBPCT is the main saving due to faster engraftment. Efficacy data taken from a multinational trial[161] (see *Table 70*).

[†] *Cost ratings: * = procedure costs only.*

[‡] *Date of assessment in brackets if available.*

TTE = time to engraftment.

TABLE 69 *Comparisons of the cost of time to engraftment for BMT vs. PBPCT for studies using the results from non-RCTs as efficacy measures*

Reference	Entry years	Disease	Type of evaluation	Costs included†	Method for determining total resources used	End-points	No. of patients	Outcomes		Details of sensitivity analysis	Comments
								Cost‡	Cost as 1993 US$		
Russell and Pacey, 1992[162] (letter)	1988–92	NHL recurrent	Costing	*	Actual cost (may be prospective for PBPCT)	TTE	23	BMT: £15,200 PBPCT: £11,400	BMT: $24,849 PBPCT: $18,637		There are few details of methods or costs. Only four patients in the in PBPCT cohort.
Duncan *et al*, 1996[163] (full paper)	1988–95	MM	Cost minimisation	*	Retrospective costs	TTE	53	BMT: £11,026 PBPCT: £7995	BMT: $14,977 PBPCT: $10,860	Looked at length of hospitalisation, cost of stem cell harvest and change in BNF prices. In all cases PBPCT was cheaper	Faster engraftment resulted in decreased duration of hospital stay.
Faucher *et al*, 1994[164] (full paper)	1989–93	NHL HD Advanced breast/ adjuvant treatment	Costing	*	Retrospective Actual usage	TTE + 30 days after discharge	56	(1992) BMT + GCSF: US$25,520 BMT: US$24,510 PBPCT + GCSF: US$19,770	BMT + GCSF: $26,284 BMT: $25,243 PBPCT: $20,361	Conclusions not affected by changes in the discount rate or room costs/day	Comparison between BMT with or without growth factor and PBPCT. Patients were treated in France. PBPCT gives shorter time to engraftment.
Knechtli *et al*, 1994[165] (abstract)	1991–93	NHL HD MM	Costing	*S	Retrospective costs	TTE	17	BMT: £12,025 PBPCT: £12,160	BMT: $18,877 PBPCT: $19,089		Similar costs in both. Back-up bone-marrow harvests were stored for the PBPCT group and colony stimulating factors were widely used.
Ager *et al*, 1995[166] (full paper)	1992–93	NHL HD recurrent	Costing	*	Retrospective costs	TTE	46	BMT: £11,080 PBPCT: £8709	BMT: $16,723 PBPCT: $13,145		PBPCT cheaper and engraftment faster.

† *Cost ratings: * = procedure costs only; *S = procedure costs + set-up costs.*
‡ *Date of assessment in brackets if available.*

Superscript letters cross-reference to the comments column.

BNF = British National Formulary; MM = multiple myeloma.

continued

TABLE 69 contd *Comparisons of the cost of time to engraftment for BMT vs. PBPCT for studies using the results from non-RCTs as efficacy measures*

Reference	Entry years	Disease	Type of evaluation	Costs included†	Method for determining total resources used	End-points	No. of patients	Outcomes: Cost‡	Outcomes: Cost as 1993 US$	Details of sensitivity analysis	Comments
de Arriba *et al*, 1996[167] (full paper)	1992–94	Various	Costing	*	Retrospective costs	TTE	22	(1994) BMT: Pts 2,992,000 PBPCT: Pts 2,551,000 BMT + PBPCT: Pts 2,824,000	BMT :$24,109 PBPCT: $22,756 BMT + PBPCT: $20,556		BMT was compared with PBPCT and with BMT + PBPCT. Paper is in Spanish.
Faucher *et al*, 1995[168] (abstract)	1992–94	Advanced breast/ adjuvant treatment	Costing	*	Retrospective Actual usage	TTE	39	BMT: US$25,000 PBPCT: US$21,000	BMT: $24,375 PBPCT: $20,476		PBPCT less expensive and engraftment was faster with PBPCT. Short-term QoL advantage in PBPCT arm. There are very few details of methods of economic analysis used. It is probable that some of these patients are included in Faucher *et al*, 1994[164] study listed above. All patients were treated with growth factors.
Rio *et al*, 1996[169] (full paper)	1993–94	HD MM	Costing		Retrospective Actual usage	Cost of treatment to 100 days after transplant	23	(1994) BMT: FF 293,295 PBPCT: FF 289,799	BMT: $43,198 PBPCT: $42,683	–	Patients treated in France. Authors comment that > 3 times as many BMT patients were discharged from hospital with neutrophil counts < 0.5 x 10^9 than were PBPCT patients, although no. of days in hospital with fever was similar in both groups.

† *Cost ratings: * = procedure costs only; *S = procedure costs + set-up costs.*
‡ *Date of assessment in brackets if available.*

Superscript letters cross-reference to the comments column.

MM = multiple myeloma.

continued

TABLE 69 contd *Comparisons of the cost of time to engraftment for BMT vs. PBPCT for studies using the results from non-RCTs as efficacy measures*

Reference	Entry years	Disease	Type of evaluation	Costs included†	Method for determining total resources used	End-points	No. of patients	Outcomes: Cost‡	Outcomes: Cost as 1993 US$	Details of sensitivity analysis	Comments
Shore *et al*, 1996[170] (abstract)	–	Not stated	Costing	*	Retrospective	TTE	37	BMT: Can$24,666 PBPCT: Can$14,699[a]	BMT: $18,860 PBPCT: $11,240		[a] Cost of PBSC given as a range Can$14,171–15,228. Canadian study.
Julia *et al*, 1995[171] (full paper)	–	Various	Costing	*	Retrospective costs	TTE + 30 days after discharge	20	(1994) BMT: Pts 1,997,000 PBPCT: Pts 1,736,000	BMT: $16,092 PBPCT: $13,989		Quotes an abstract in Spanish, from conference proceedings, which calculated the cost of BMT as Pts 4,039, 000 and the cost of PBPCT as Pts 3,443,000. Paper is in Spanish.
Uyl-de Groot *et al*, 1994a[172] (full paper)	–	Solid tumours and lymphoma	Costing	*	Retrospective Actual usage	TTE	66	(1992) BMT + GCSF: US$32,443 BMT: US$30,592 PBPCT: US$21,809	BMT + GCSF: $33,414 BMT: $31,508 PBPCT: $22,461	Looked at changes in the cost of hospital stay, transfusions and GCSF. PBPCT remained the cheapest option	Patients treated in The Netherlands. Authors note that overall costs were significantly lower in the PBPCT group because of decreased time to engraftment which in turn decreased number of transfusions and the duration of hospital stay.
Uyl-de Groot *et al*, 1994b[173] (full paper)[b]	–	MM	Costing	*S	Retrospective Actual usage	TTE	26	With PBPCT: US$17,905 Without PBPCT: US$32,223	With PBPCT: $18,441 Without PBPCT: $33,108		[b] Study comparing the time to engraftment for HDT ± PBPCT. Analysis was HDT ± PBPCT rescue. Slower recovery without PBPCT rescue raised hospital costs.

† *Cost ratings: * = procedure costs only; *S = procedure costs + set-up costs.*

‡ *Date of assessment in brackets if available.*

Superscript letters cross-reference to the comments column.

MM = multiple myeloma.

Chapter 18

BMT versus PBPCT

Introduction

PBPCT is increasingly used as an alternative to BMT for several reasons. Harvesting of PBPCs is thought to be more acceptable to the patient since no general anaesthetic is required and the procedure is less invasive. The use of haematopoietic growth factors has made it possible to mobilise large numbers of PBPCs to allow serial high-dose treatments to be carried out, and is thought to result in faster engraftment. It may also be possible to obtain PBPCs from patients whose bone marrow is unsuitable for harvesting owing to previous therapy or malignant infiltration. However, at present there is little data comparing the efficacy of BMT with PBPCT in terms of survival and PFS, nor information about the long-term effectiveness of PBPC renewal capacity.

Methods

The search strategies in chapter 2 were used. The search strategies only identified studies which included patients being treated for one of the malignancies addressed in this review so it is possible, although unlikely, that randomised studies including only patients with non-malignant conditions or malignancies not addressed in this review have not been identified.

Results

Five studies were identified (*Table 70*): one[174] included patients with germ-cell tumours, two[161,175] included patients with lymphoma (both HD and NHL), one[160] included patients with solid tumours and lymphomas, and one trial[176] made no mention of the type of patients treated. Three[160,161,174] trials used growth factors to mobilise the peripheral blood stem cells, one[176] used growth factor to mobilise both bone marrow and PBPC, and one[175] used no mobilising agents. All trials investigated autologous transplantation and across all trials more than 262 patients were randomised between 1989 and 1994.

Time to haematopoietic recovery

Three publications[160,161,174] reported a conventionally significant decrease in the time to platelet and neutrophil recovery with PBPCT, and whereas two publications[175,176] reported no evidence of a difference in haematopoietic recovery. In two papers[160,161] the authors commented that there was no evidence of a difference in the number of bleeding episodes between the two groups. No evidence of a difference in the number of febrile episodes was reported in two studies,[161,174] whilst for a third study[160] it was reported that there was a significant decrease in the duration of febrile episodes with PBPCT, although no comment was made on the incidence of the episodes.

Time to discharge from hospital

Two publications[160,161] reported a conventionally significant decrease in the time to hospital discharge with PBPCT, and two[174,175] reported no evidence of a difference. The other publication[176] reported no data on this outcome.

PFS or survival

No trial found evidence of a difference in overall survival[161,175] or PFS.[160,174,175]

Discussion

Of the five trials identified, for three[160,161,174] it was concluded that the use of PBPCs decreased the time to haematological recovery with no compromise in the efficacy of HDT/PCT. Although no publication reported differences in survival or PFS, it should be acknowledged that the trials were small and that the trial data were immature.

In two trials[175,176] no evidence was found of differences between PBPCT and BMT in any of the clinical parameters measured. For one of these trials[175] the authors comment that this may be because no growth factors were used for the mobilisation of the PBPCs. However, the trial[175] was also small, randomising only 28 patients, and therefore only large differences would have been detected. In the second of the trials that found no difference between PBPCT and BMT[176] both the bone marrow and PBPC were primed with growth factor and the authors conclude that it is the use of growth factors before cell harvesting, not the source of the stem cells, that determines the speed of engraftment.

There was considerable clinical heterogeneity in the patient populations included in the trials. The patients were also in various stages of disease treatment, with different previous exposure to cytotoxic drugs.

Overall it appears that PBPCs mobilised using haematopoietic growth factors shorten the time to engraftment when compared with resting bone marrow, with no apparent effect on survival.

Whilst the evidence for more rapid engraftment with mobilised PBPCs is strong, there is a lack of information concerning long-term outcome, particularly with respect to control of malignancy. For this reason further careful studies are required to determining the relative merits of the two approaches. Ideally these studies should be in randomised trials, and it will be important to have longer follow-up on the trials that have already been conducted.

TABLE 70 *RCTs comparing the haematopoietic recovery times of BMT and PBPCT*

Reference	Entry years	Disease eligibility	No. of patients			TTE						Hospital stay			Survival		PFS		Comments
			Total	BMT	PBPCT	Platelet count			Neutrophil count										
						Median (range) time to > 20 x 10^9/l (days)		Stats in paper	Median (range) time to > 0.5 x 10^9/l (days)		Stats in paper	Median (range) (days)		Stats in paper	1 year BMT: PBPCT	Stats in paper	1 year BMT: PBPCT	Stats in paper	
						BMT	PBPCT		BMT	PBPCT		BMT	PBPCT						
Beyer *et al*, 1995[174] (full paper)	1991–93	Relapsed or refractory germ cell tumours	47	23	24	17	10	$p = 0.01$	11	10	$p = 0.01$	19 (13–51)	16 (11–33)	$p = 0.16$ (Mann Whitney)	–	–	54:43	$p = 0.39$	Stem cells mobilised with growth factors. Authors conclude that the use of PBPCT results in sustained haematological recovery which occurs more rapidly than with BMT. No difference in the number of febrile days.
Schmitz *et al*, 1996[161] (full paper)	1993–94	Advanced HD or high-grade NHL	58	31	27	23 (13–56)	16 (8–52)	$p = 0.02$	14 (9–25)	11 (9–38)	$p = 0.005$	23 (14–65)	17 (13–53)	$p = 0.002$	87:86[a]	[b]			Stem cells mobilised with growth factors. Authors comment that PBPC transfusions significantly reduced the time to haematopoietic recovery and this led to an earlier discharge from hospital. No differences in the number of febrile episodes or heaemorrhagic events was observed. [a] These data are taken from a graph which is labelled in days, but text implies that it is in months. [b] 'No obvious difference' reported in paper.

Superscript letters cross-reference to comments column.

continued

TABLE 70 contd *RCTs comparing the haematopoietic recovery times of BMT and PBPCT*

Reference	Entry years	Disease eligibility	No. of patients			TTE						Hospital stay			Survival		PFS		Comments
			Total	BMT	PBPCT	Platelet count			Neutrophil count										
						Median (range) time to > 20 x 10^9/l (days)		Stats in paper	Median (range) time to > 0.5 x 10^9/l (days)		Stats in paper	Median (range) (days)		Stats in paper	1 year BMT: PBPCT	Stats in paper	1 year BMT: PBPCT	Stats in paper	
						BMT	PBPCT		BMT	PBPCT		BMT	PBPCT						
Hartmann *et al*, 1997[160] (full paper)	1993–94	Various solid tumours and lymphomas	129	65	64	36.5 (9–579)[c]	17.5 (1–145)[c]	$p < 0.001$	12 (6–31)	8 (3–18)	$p < 0.001$	31 (19–84)	24 (16–172)	$p < 0.001$	–	–	68:58	$p < 0.2$	Stem cells mobilised with growth factors. Authors comment PBPCT is superior to BMT for both solid tumours and lymphomas in terms of haematological recovery. No evidence of a difference in the number of haemorrhages in each group; febrile events were shorter in the PBPCT group. No compromise in the probability of event-free survival at a median follow-up of 20 months. [c] Time to > 50 x 10^9/l
Weisdorf *et al*, 1997[175] (full paper)	1989–	Chemo-sensitive HD and NHL	28 55 (A)	13	15	24 (13–182)[d]	58 (18–104)[d]	$p = 0.34$	23 (11–53)	30 (11–104)	$p = 0.13$	33 (19–52)	43 (21–69)	$p = 0.13$	34:53 2 years	$p = 0.89$	–	NS	Stem cells collected without growth factor mobilisation. Authors comment that there is no advantage for PBPCT over BMT in this study, but add that this disputes findings with growth factor-mobilised stem cells. [d] Time to platelet independence: the time to no platelet transfusions for ≥ 15 days.

Superscript letters cross-reference to comments column.
A = assigned.

continued

TABLE 70 contd *RCTs comparing the haematopoietic recovery times of BMT and PBPCT*

Reference	Entry years	Disease eligibility	No. of patients			TTE						Hospital stay			Survival		PFS		Comments
						Platelet count			Neutrophil count										
						Median (range) time to > 20 x 10^9/l (days)		Stats in paper	Median (range) time to > 0.5 x 10^9/l (days)		Stats in paper	Median (range) (days)		Stats in paper	1 year BMT: PBPCT	Stats in paper	1 year BMT: PBPCT	Stats in paper	
			Total	BMT	PBPCT	BMT	PBPCT		BMT	PBPCT		BMT	PBPCT						
Janssen *et al*, 1994[176] (letter)	1992–	–	–	–	–	22 (7–52+)	23 (7–52+)	$p = 0.32$	16 (13–44)	15 (12–29)	$p = 0.23$	–	–	–	–	–	–	–	Collection of both stem cells and bone marrow was preceded by the administration of growth factor. There is ittle information in the letter, and no indication of the type of patients included. Authors state that these results are preliminary.

Superscript letters cross-reference to comments column.

Chapter 19

Review: long-term toxicity

Introduction

As the use of HDT/PCT has increased, and the early regimen-related mortality has been reduced, evidence has emerged that HDT/PCT may be associated with significant long-term toxicities. These have been observed in patients undergoing both allogeneic and autologous transplantation.

Many research groups have identified secondary myelodysplasia, leukaemia, or other second malignancies, particularly NHL, in survivors of both PBPCT and BMT (*Table 71*).[177–179] However, the precise incidence of these complications is unclear. Although high-dose chemotherapy (particularly alkylating agents) and total body irradiation (TBI) have been implicated, it is possible that treatment given before the HDT may be partly responsible for the risk of secondary cancer, as is well documented for HD.

Other frequently documented long-term toxicities include infertility and impairment of immune function associated with B and T lymphocyte disorders[180,181] and general health. The functional and employment status of survivors of BMT have also been studied.[182]

Methods

The search strategies set out in chapter 2 were used. The search strategies were designed to identify those studies that have investigated BMT in each malignancy included in this review. Therefore, it is possible that eligible papers addressing the general question of long-term toxicity, which have not been tagged in the electronic databases with a disease-specific label nor have a disease mentioned in the abstract text, have not have been identified by the search strategies used.

Results

No randomised studies addressing the comparative long-term side-effects of HDT/PCT and CC were found and only four cohort studies were identified. The findings of these cohort studies, the results of which are summarised in *Table 72*, are subject to the same biases as those of non-randomised efficacy studies and their results should be viewed with similar caution.

Discussion

As is the case with the efficacy of HDT/PCT, many hundreds of papers have reported the incidence of long-term toxicities in cohorts of patients receiving HDT/PCT. Although these papers have been able to identify the types of long-term toxicity that might be expected from HDT/PCT (see below), they are unable to give any reliable information about whether the incidence is significantly higher than that experienced by similar patient populations treated with CC.

The types of toxicity reported fall into two categories, those that can be attributed to chronic GVHD (or its treatment), which occurs after allogeneic transplantation, and those probably caused by the high-dose radiotherapy and chemotherapy itself, which will occur regardless of the type of transplant used. Several of the toxicities are generally attributed to the administration of TBI, and it is thought that the incidence and severity of many of these complications may diminish if the TBI is fractionated rather than administered as a single fraction.

Because of the lack of randomised evidence, it is not possible to draw any conclusions about the relative incidences of long-term toxicities of HDT/PCT compared with CC. Further research in this area is urgently needed, including the long-term follow-up of patients entered into clinical trials of HDT/PCT versus CC.

TABLE 71 *Long-term toxicities associated with HDT and BMT together with likely causes*

Toxicity	Likely cause(s)
Secondary malignancies	Chemotherapy (particularly alkalyting agents), radiation and the prolonged use of immunosuppression (for prevention of GVHD)
Infections	Chronic lung damage as a result of GVHD and following radiation
Pulmonary disorders including interstitial pneumonitis, obliterative bronchiolitis	Chemotherapy, radiation
Liver dysfunction	Chronic GVHD
Malabsorption with associated weight loss and diarrhoea	Chemotherapy, radiation
Growth retardation	Radiation, chronic GVHD, prolonged use of corticosteriods
Infertility/gonadal malfunctioning	Radiation, chemotherapy
Renal dysfunction	Nephrotoxic chemotherapy, radiation
Osteoporosis	Prolonged use of steroids, premature menopause, chronic GVHD
Aseptic osteonecrosis	Chronic GVHD
Neurological including polyneuropathies, isolated dysfunction of peripheral nerves	Severe chronic GVHD, herpes zoster infection
Thyroid dysfunction	Radiation
Myelodysplasia	Chemotherapy, radiation
Psychological disorders	Undetermined
Cataracts	Radiation
Dry eyes and mouth	Radiation or GVHD
Skin disorders including de-pigmentation, poor hair and nail growth, lichenoid changes in mucosal membranes	Chemotherapy, radiation, GVHD, infection
Premature dental deterioration	Chemotherapy, radiation
Transfer of conditions from donor to recipient	Following allogeneic transplantation

TABLE 72 *Summary of cohort studies comparing the long-term toxicities of HDT with those of CC*

Reference	Type of long-term toxicity investigated	No. of patients HDT:CC	Summary of findings
Mumma *et al*, 1992[183] (full paper)	Psychological	21:49	There were no differences between the two treatment modalities in terms of psychosexual function (as measured by four scales of the Derogatis Sexual Functioning and one subscale of the Psychological Adjustments to Illness Scale), even though women in the HDT cohort had a greater degree of gonadal dysfunction than those in the CC cohort (80% vs. 16%, respectively).
Molassiotis *et al*, 1996[184] (full paper)	Psychological	91:73	QoL was compared for a group of 91 BMT recipients and 73 CC recipients in a retrospective descriptive study. There was little overall difference between the two cohorts: the only reported difference was that patients who had received CC experienced a greater degree of depression.
Mashberg, 1989[185] (abstract)	Psychological	21:19	The psychological adjustment of patients receiving conventional or no chemotherapy for chronic myelocytic leukaemia was compared with that of patients receiving HDT/PCT. The author reported that there were no statistically significant differences between the two groups in psychological adjustment or psychological distress.
Chessells *et al*, 1986[20] (full paper)	General	5:12	This paper reported on the long-term outcome of the surviving patients included in a retrospective study of children with ALL in second remission who received allogeneic BMT or CC. At follow-up, in the HDT group four children were growth hormone deficient and required oestrogen supplements. Of these four children one also had ovarian failure and two others had evidence of compensated hypogonadism. Two children had difficulties at school. In the CC cohort 11 of the 12 children were in full-time education, one of whom was experiencing learning difficulties. The other patient had developed an encephalopathy during treatment and at follow-up was receiving anticonvulsants and required special schooling.

Chapter 20

Review: cord-blood transplantation

Introduction

Blood from the umbilical cord was first suggested as a potential source of progenitor cells in 1983, and following testing in animal models the first human transplantation using cord-blood cells from a sibling donor was carried out for a child with Fanconi anaemia in 1988.[186] The difficulties of finding matching donors for allogeneic transplantation and the potential advantages of cord blood as a source of stem cells have encouraged the establishment of cord-blood banking and transplantation programmes in several countries.

Cord blood is collected from the placenta via the umbilical vein after delivery of a baby and cutting of the cord. In this way, the cells are obtained without risk or detriment to either the mother or child. Apart from avoiding an invasive procedure, there are other potential advantages of cord blood as a stem cell source: the naive immune repertoire of the neonatal system may pose a lesser risk of GVHD than other unrelated donor transplants, and the low rate of viral carriage may reduce the risks of infections with agents such as Epstein–Barr virus and cytomegalovirus.

The limitations of cord-blood transplantation have principally been logistic, requiring facilities for collection and cryopreservation of the cells to be available at the time of delivery. For sibling transplants this can be arranged in advance, but for unrelated donors a bank of cord blood is required with information concerning histocompatibility and microbiological screening obtained at the time of collection. Once set up, however, blood banks could decrease the cost and inconvenience of harvesting and transporting stem cells. Perhaps the major constraint on the procedure has been the limited number of cells that can be obtained from a single placenta which will determine the maximum size of patient for whom the procedure could be used.

Methods

The search strategies set out in chapter 2 were used.

Results

All publications identified, in which the use of cord-blood transplantation for patients undergoing HDT/PCT for malignancy was described, concerned the feasibility of the procedure and the complications observed in patient series. No studies have compared differences between the *in vivo* characteristics of transplanted cord blood and other sources of progenitor cells, or between sibling and unrelated donors.

The majority of papers reported the results of cord-blood transplantation in one or a few patients, describing the procedure and the engraftment characteristics. Summaries of case series of more than ten patients are tabulated (*Table 73*).

Single procedures and small cases series with sibling donors have been described for childhood ALL,[187–190] childhood CML,[191–195] childhood lymphoma[196] and childhood AML.[197] The largest series of 44 sibling donor transplants was reported from the International Cord Blood Transplant Registry.[198]

Unrelated donor procedures have also been described in single cases and small case series for children with acute leukaemia[199,200] and in single cases of adults with AML[201] and CML.[202–204] Two large series of unrelated cord-blood transplants have been described,[205,206] each including transplants for both malignant and non-malignant conditions (*Table 73*).

The cohort studies using cord blood identified above do not, of course, represent the total number of cord-blood procedures performed; patients with genetic disorders and children with solid tumours other than those addressed in this review have also successfully received transplants.

Discussion

Although the first transplantation was performed less than a decade ago,[186] cord-blood transplantation is already widely regarded as a viable clinical procedure of considerable promise

and importance. In 1992, the first US pilot public blood bank was established at the New York Blood Center which today aims to store 20,000 units of blood (one unit being the blood collected from one placenta/ umbilical cord). In the UK, the National Blood Service/Scot Blood in conjunction with other organisations have established, or are in the process of establishing, five cord-blood banks which aim to have banked 20,000 units of blood in the next 2–3 years for both transplantation and research purposes (Donaldson C, Cord Blood Bank, Bristol: personal communication, 1997).

In Europe, a collaborative research project, Eurocord, which is affiliated to the EBMT, was initiated in 1995 and currently has 5000 units banked. Eurocord has a number of aims:

- to standardise the methods of collection, testing and cryopreservation of cord blood
- to study the properties of haematopoietic progenitors present in cord blood including expansion and gene transfer
- to establish a European depository of cells, DNA and serum for study of infectious diseases and genetic disorders in a series of 20,000 cord-blood collections performed in different European countries
- to establish a European registry of patients treated with cord-blood transplants
- to design prospective protocols comparing cord-blood transplantations with transplantations of haematopoietic stem cell from other sources.

Although these banking initiatives are already well underway, many ethical and logistic considerations concerning the storage and use of cord blood have yet to be fully examined. Possibly the most controversial issue is that of ownership and whether donated blood in a public cord-blood bank should be available to any suitable recipient and therefore not guaranteed to be available to the donor (child) if required in later life. It is also considered necessary to ensure follow-up of both mother and child to detect any genetic or infectious disease not detected at birth. However, experience in Belgium has shown that follow-up compliance by mothers at 4 months can be low and in some banks only just over half of samples have been fully validated.[207] Issues involving consent concern both the use of cord blood in clinical procedures and for research purposes; ideally informed consent should be given by a mother prior to delivery for both types of use. The number of units stored in a public cord-blood bank must be sufficiently large to ensure a high chance of finding a match for all patients regardless of genetic background, and it is essential that banked cord blood is donated from a racially diverse population which reflects the population that the cord-blood bank is serving. In addition, little is known about the long-term viability of cyropreserved cord blood and therefore no information is available about the maximum length of time donations can be stored.

The cost of establishing and maintaining a cord-blood bank has yet to be fully established. The charge for private cord-blood banking in the US is approximately $1500 for the first year and $95 for each subsequent year of storage,[208] whereas in Belgium the cost of banking one fully validated unit of cord blood is reported to be US$650.[207] The overall cost of any bank will depend largely on the number of units banked and the length of time for which it is determined that blood can be stored.

There remain many unanswered clinical questions concerning the use of cord blood. One of the potential advantages of this type of transplantation is the likely decreased level of GVHD. While this may lower the initial treatment-related toxicity it could also mean a decrease in the GVL effect, which may in some diseases increase the relapse rate. Because of the number of stem cells contained in a single unit of cord blood, this type of transplant is thought to be most suitable for children. *Ex vivo* expansion of the stem cells is one possible means of increasing the number of cells available and potentially of widening the applicability of cord blood; it also raises the possibility of establishing colonies of genetically rare stem cell lines. This approach, however, is still highly experimental and the viability of *ex vivo* expanded stem cells has yet to be established. Some of these and other questions of efficacy are likely to be addressed following a grant of US$30 million, in April 1997, by the US National Heart Lung and Blood Institute to seven centres in the USA to coordinate Phase III trials in cord-blood transplantation.[209]

Further research, both laboratory and clinic based, is needed to establish what role, if any, cord blood should play in the treatment of malignancies and other conditions. If resources are to be used most effectively it is essential that the efficacy of cord blood in clinical practice is tested in appropriate RCTs and that its use does not become established on the basis of promising, but unreliable, observational studies.

TABLE 73 *Summary of case series of cord-blood transplantation including more than ten patients*

Reference	No. of patients		Age range	Weight range (kg)	Summary of paper
	Malignant	Non-malignant			
Wagner *et al*, 1995[198] (full paper)	25	–	8 months–16 years	7.5–50	The number of nucleated cells in the grafts ranged from 1 to 33 x 10^7/kg (median 5.2). Seven transplants failed to engraft; in six cases the recipients weighed more than the median 18 kg. The median time to neutrophil recovery to 500 x 10^6/l was 22 days (range 12–46 days) and this did not appear to be significantly shortened by the use of colony-stimulating factors in 25 patients. Median time to platelet recovery to 50 x 10^9/l was 49 days (range 15–117 days). There was no apparent relationship between the engraftment times and numbers of cells in the grafts. No patient developed severe GVHD, although one of five patients given HLA-3 antigen disparate grafts developed grade III GVHD. Two cases of chronic GVHD were seen, one in a patient with an HLA-identical graft and one in a patient with an HLA-1 mismatch graft.
Wagner *et al*, 1996[205] (full paper)	13	5	1 month–21 years	3.3–79	The number of nucleated cells infused ranged from 1.4 to 40 x 10^7 cells/kg. Five patients died before engraftment but in the remainder neutrophil recovery to 500 x 10^6/l took a median of 24 days (range 16–53 days). Platelet recovery was more prolonged, with a median time to 50 x 10^9/l of 67 days (range 55–120 days) and in three cases, patients remained dependent upon platelet transfusions. Although the authors state that engraftment occurred in the largest patient, none of five patients weighing > 30 kg regained adequate haematopoiesis: there were three toxic deaths and two patients remained platelet transfusion-dependent. There were only two cases of severe (grade III/IV) GVHD despite disparity of 1–3 HLA antigens in 11 patients.
Kurzberg *et al*, 1996[206] (full paper)	21	4	10 months–23 years	7.5–79	24 of 25 patients were discordant for 1–3 HLA antigens. Evidence of engraftment occurred in 23 of the patients (median time to 500 x 10^6/l was 22 days; range 14–37 days). For 16 evaluable patients median time to platelet recovery was 56 days (range 35–89 days). The authors note that complete haematopoesis occurred in more than half of all patients. Acute severe (grade III or IV) GVHD occurred in only two of 21 evaluable patients.

Chapter 21

General discussion

Treatment using HDT/PCT has been under investigation for more than 30 years and has, for some diseases, become established as a routine component of treatment (see EBMT report summary – appendix 5). Despite the publication of hundreds of case series and cohort studies involving thousands of patients, few randomised or controlled trials have compared the HDT/PCT approach with standard therapy. Consequently, the use of HDT/PCT is guided by little reliable evidence. As for any potentially toxic and costly treatment, it is important to determine whether or not HDT/ PCT is more effective than standard therapy, and to establish its associated benefits and detriments, as a basis for deciding whether it should have a role in routine clinical practice. The purpose of carrying out this systematic review was to synthesise the available evidence in a number of key cancers to establish the current state of knowledge about HDT/PCT.

Scope of this review

This report reviews the published literature comparing HDT/PCT with conventional treatment in a number of cancer sites. Owing to time constraints, and as planned in the protocol, no unpublished data were reviewed. The literature searches for prospective RCTs and CCTs, on which the review is based, are complete to June 1997. This means that many but not all (because of the speed of bibliographic database indexing) of the trials published by the end of 1996 will have been included, together with some more recent publications that have appeared in high-profile journals that are indexed quickly by bibliographic databases.

The review has focused on the results of RCTs owing to the many potential problems and biases associated with non-RCTs. However for the acute leukaemias, controlled trials of allogeneic transplantation, using pseudo-random methods of treatment allocation, have also been considered. Other published cohort studies are tabulated to provide additional background information only and no conclusions are drawn from these.

The disease sites studied were selected on the basis of previous research activity, current practice and potential future clinical and economic impact based on the incidence of each disease.

The end-points reviewed were survival and PFS as these were judged to be clinically relevant across all disease sites and the most commonly reported outcomes in individual studies. Although progression is a potentially subjective and therefore 'softer' end-point than survival, the time alive without evidence of disease is an important outcome for patients which may have significant impact on their quality of life. No formal assessment of quality of life as an outcome was made as few individual studies reported this information and because of the difficulties associated with comparing and summarising such data, measured on different scales at different time-points and in different patient populations, across individual studies.

Constraints and caveats

The approach used in this systematic review has a number of limitations which must be borne in mind when interpreting the results.

As the review is based on the published literature only, it may suffer from publication bias, whereby trials with positive results are more likely to be published than those with negative or inconclusive results. Thus the published literature may be biased in favour of HDT/PCT. A number of completed but as yet unpublished trials have been identified for which the results were not available to be included in this review. Since time constraints did not allow data to be collected from closed, unpublished trials, no formal assessment can be made as to whether or not publication bias influences the findings of this review.

Owing to incomplete reporting of trials, the combined analyses presented here are often based on only a proportion of even those few patients entered into prospective trials. Not all publications presented the required data at one or more of the time-points studied, and so the trials included in the combined analyses are not always consistent over time. In addition, quantitative review was restricted to fixed time-point analyses which is

not the most informative method of summarising time-to-event data such as survival or PFS. Thus it is important that the numerical syntheses presented are interpreted cautiously and used only as a rough indication of the possible benefits or detriments of HDT/PCT.

Nonetheless, this report presents a systematic review which, within the constraints of the approach, is believed to represent a comprehensive and reliable summary of the current published literature.

ALL

HDT including PCT has a relatively long history in the treatment of ALL. An advantage of the approach is that it may offer a much shorter duration of therapy with approximately 3 months being required to undergo HDT/PCT compared with about 2 years for standard maintenance treatment.

Childhood ALL

At presentation, treatment for paediatric ALL with CC is very effective, and consequently most studies have concentrated on the use of HDT with allogeneic transplantation in the consolidation of second complete remission. Historically, transplantation has used donor grafts, usually from a sibling when there is a 25% chance of achieving a match. Although a great many case series and cohort studies have been reported, few prospective trials have addressed the value of allogeneic transplants. No RCTs have been published, nor as far as is known are any proposed. This is almost certainly a result of the difficulties of consent when randomising children, especially when this takes place after identifying a matching donor. Two small CCTs in which treatment allocation was based on donor availability have been published, one in first remission and the other in second remission. These accrued 111 and 45 patients, respectively. Given the very few patients included in these studies there is currently no reliable evidence concerning the use of HDT plus allogeneic transplantation in comparison with conventional therapy in this situation. Although used widely in clinical practice, it is not clear from the results of the CCTs available whether such treatment improves survival or PFS in children with ALL.

Although this is an area in which it is undoubtedly difficult to conduct RCTs, it may be possible to derive useful information from well-designed CCTs. In future more careful consideration should be given to study design. Indeed, with more appropriate analysis (comparing those who did with those who did not receive a transplant for all tissue-typed patients), cohort studies such as those shown in *Table 7* could be conducted as CCTs. Thus information gathered from the same children could be used to obtain a more reliable answer to this important question. The setting up of further CCTs and participation in the currently on-going trial should be encouraged.

Until recently the use of autologous transplantation has been little investigated, although a potential advantage of this approach is that it may offer a much shorter duration of therapy. However, given that the majority of patients do not have an available donor and that routine practice involves treatment with conventional therapy, RCTs are feasible and participation in the two on-going studies should be supported.

Adult ALL

For adults with ALL, the prognosis is generally poor and HDT/PCT has been investigated largely as consolidation of first remission. Three RCTs of HDT with autologous transplantation have been published. In total these three studies accrued 213 patients. However, the reporting of these small trials is incomplete and currently there is insufficient evidence on which to base firm conclusions concerning the use of HDT and autologous transplantation in adult ALL. Three trials of autologous transplantation are on-going.

For similar reasons to those described above for childhood ALL, RCTs of HDT including allogeneic transplantation are difficult and no such published trial was identified. A total of five CCTs, involving a total of 462 patients, which compared HDT plus allogeneic transplantation with CC in adult ALL have been published. These are incompletely reported with only one trial presenting information on survival. Although all trials favour the use of HDT in terms of PFS, such results must be interpreted with caution owing to the potential bias associated with non-randomised studies. Further trials involving more patients are required to confirm or refute the observations to date and recruitment to the two on-going and future RCTs should be supported.

AML

A meta-analysis of individual patient data has already been completed by the AML Collaborative Group. This will provide a more reliable assessment

than this review of the effectiveness of HDT/PCT in treating AML in first remission. Therefore, the results presented here should be regarded as an interim summary to be superseded by the results of the AML Collaborative Group project when they enter the public domain.

Childhood AML

Paediatric AML carries a poor prognosis and treatment with CC has yielded disappointing results. Consequently, the use of HDT/PCT in the consolidation of first remission has been investigated. For the same reasons as discussed for ALL, randomised comparisons involving allogeneic transplantation have been difficult and no such study was identified. However for paediatric AML the use of HDT plus autologous BMT has been compared with CC for the consolidation of first remission in four published RCTs, which in total randomised 712 children. Although combined analyses appear to favour CC, much of the published data is immature and there is no good evidence of a difference between the two types of therapy. Two RCTs are currently on-going and participation in these trials should be encouraged.

Five published CCTs which compared HDT and allogeneic transplantation with conventional therapy in total accrued over 1000 children. Reporting of these trials was incomplete and allowed no firm conclusions regarding overall survival to be drawn. Although all trials with allogeneic rescue favoured HDT/PCT in terms of PFS, these results must be interpreted cautiously given the potential bias associated with non-randomised studies. Further data will be available following the completion of the four CCTs currently in progress and entry into these trials should be supported.

Adult AML

In adult patients four RCTs including a total of 553 individuals have compared HDT and autologous transplantation with conventional therapy in the consolidation of first remission. Although there was no good evidence of a difference in survival between the two treatments, there was some suggestion of a benefit from HDT/PCT in terms of PFS, with all but one trial favouring this approach and the combined analyses reaching conventional levels of significance.

Eleven published CCTs were identified which compared HDT and allogeneic transplantation versus conventional therapy in the consolidation of first remission. These included almost 1000 patients. Reporting of trials was incomplete, with just over half of the publications presenting survival and/or PFS data. The individual trials yielded inconclusive and conflicting results for survival. Although the combined analyses appear to suggest a survival benefit of HDT/PCT at 4 years, this is driven largely by the results of a single study for which the results are extreme. Without this trial, there is no evidence of a significant difference in survival between the two treatments. For PFS there is some evidence of a benefit from HDT/PCT and combined analyses reach conventional levels of significance.

Although the published results may appear promising, no firm conclusions can be drawn on the role of HDT/PCT in the treatment of adult AML. Further work is required to determine whether or not HDT with either autologous or allogeneic support is more effective than conventional therapy in the treatment of first remission adult AML. The meta-analysis of individual patient data will be important in this respect. However, it will not answer all questions and recruitment into the three on-going prospective trials should be encouraged.

CML

Owing to poor prognosis, lack of effective conventional therapies, and a perceived benefit of HDT/PCT from case series and cohort studies, HDT including allogeneic transplantation is widely regarded as standard therapy for younger CML patients. There has been a reluctance to conduct prospective trials and no published RCTs or CCTs were identified. In the absence of such trials the magnitude of any potential benefit or risk associated with HDT and allogeneic transplantation cannot be reliably determined.

For patients without a suitable donor who are fit to tolerate HDT, autologous transplantation may be a viable option for prolongation of the chronic phase. Two large RCTs investigating HDT with autologous support are in progress which between them plan to accrue 1550 patients. Recruitment to these trials should be supported.

CLL

As CLL is largely a disease of the elderly, HDT/PCT is unlikely to be widely used in routine management and any potential future use is likely to be restricted to the small proportion of young patients. Although HDT with PCT has been shown to be feasible, it remains an experimental

procedure which currently plays no role in routine clinical practice. If, in future, HDT/PCT is to be considered as a potential treatment option, then further research is required including appropriate prospective evaluation in RCTs comparing the approach with best standard therapy.

Non-Hodgkin's lymphoma

HDT/PCT is widely used as a component of standard salvage therapy for relapsed or refractory intermediate- or high-grade NHL. Although there is little reliable evidence supporting its use in this context, in the absence of further randomised trials the use of HDT/PCT as salvage therapy is likely to remain a standard approach.

Reports on seven RCTs have been published. These trials involved patients with intermediate- and high-grade NHL at various stages of relapse and remission, the results of which are immature and often conflicting. In total these trials have included over 1000 patients. However, they have spanned treatment ranging from first-line therapy to salvage therapy and have included a number of clinically distinct types of disease. Numbers within each of the different categories were limited. Consequently it is not possible to draw any firm conclusions regarding the efficacy of HDT/PCT in treating NHL.

Several RCTs are currently in progress and should be completed within the next few years. These will add significantly to the current evidence and enable a more reliable assessment of whether or not HDT/PCT confers improved survival in aggressive NHL. Participation in such trials should be encouraged.

There is very little evidence available concerning the role of HDT/PCT in treating the more indolent low-grade NHLs. One RCT has closed recently owing to poor accrual and several others are on-going. Participation in such RCTs should be encouraged.

Hodgkin's disease

On the basis of the results of single institution and registry data, HDT/PCT is commonly used as part of standard second-line treatment for HD. There is, however, very little reliable evidence to support this policy. Only one RCT has been published, which with 40 patients randomised is much too small to allow any firm conclusions to be drawn or treatment recommendations to be made. Three on-going RCTs, two in poor-risk first remission and one in the salvage setting have been identified. Participation in these and the setting up of further RCTs should be encouraged. As young adults form a large proportion of HD patients it is particularly important that future trials address the issue of long-term toxicity.

Multiple myeloma

Although HDT with autologous transplantation is increasingly used as a component of management for younger patients, there is still little evidence from randomised trials concerning its role in treating multiple myeloma. Only two published RCTs have been identified, which with a total of 357 patients randomised are too small to allow firm or reliable conclusions to be drawn, despite potentially encouraging preliminary results. If HDT with autologous transplantation is to be considered as a widely applicable therapeutic option for multiple myeloma then it is important that further RCTs are undertaken. Two such trials are in progress to address the issue.

Solid tumours

Few trials have investigated the use of HDT/PCT in treating solid tumours and until recently the intervention was used rarely. There is now, however, an increasing trend towards the use of HDT/PCT, especially against breast cancer, which is now the most common condition for which HDT/PCT is used in the USA. Clearly it is important that appropriate research is conducted to establish whether or not HDT/PCT has a role in treating solid tumours. If the use of HDT/PCT to treat common solid tumours became widespread, it could potentially have considerable resource implications. It should, however, be appreciated that many patients are likely to be considered too old or to have disease too advanced to undergo HDT/PCT, thus restricting the potential number of procedures.

Only one RCT has been reported in germ-cell tumours and this found no evidence of a difference in outcome between HDT/PCT and standard therapy. Similar conclusions were reached for one small published trial in SCLC. No reliable evidence exists concerning the use of HDT/PCT in ovarian cancer, although two RCTs are now

on-going. For breast cancer, three RCTs including less than 200 women in total have been published and these have conflicting results. There is therefore currently insufficient evidence to conclude whether or not HDT/PCT is of benefit in treating any of the solid tumours investigated.

Further research must be a priority and enrolment of patients into RCTs should be encouraged. In breast cancer a number of RCTs are in progress which, if target accruals are met, will result in over 4500 randomisations and should allow a reliable assessment of the value of HDT/PCT in both the adjuvant and advanced settings. Somewhat fewer on-going RCTs have been identified for the other solid tumours reviewed. If HDT/PCT is to be considered as a treatment option for these tumours, the setting up and completion of RCTs must be a priority.

Cost of HDT with BMT or PBPCT

HDT/PCT is easily perceived as an expensive intervention owing to the initial cost of harvesting progenitor cells and the need to provide intensive medical support in specialist facilities. However, the true cost of HDT/PCT must be considered in relation both to the long-term consequences of treatment and the cost of treating similar patient populations with conventional therapy.

Given that the main conclusions of this review are that the role of HDT/PCT in treating most cancers remains uncertain, and that further research is required to obtain reliable estimates of clinical effectiveness, the cost-effectiveness analyses presented here should be regarded as preliminary. This review has therefore concentrated on presenting reported comparisons of the cost of treatment (together with some subsequent therapy). However, there are problems with even these comparisons because most studies of cost are both retrospective and based on very small numbers of patients. Ideally, studies would be based on long-term cost data collected prospectively for sufficiently large and comparable groups of individuals treated with HDT/PCT or conventional therapy.

The limited and potentially flawed published data available suggests that transplantation costs 1–5 times more than conventional therapy (including maintenance therapy). Comparisons of PBPCT and BMT suggest that PBPCT is less expensive.

Use of cord blood

The use of stem cells derived from the umbilical cord following birth is a relatively new and still experimental procedure. A potential advantage of the approach is thought to be the reduced risk of GVHD and the use of cord blood also removes the cost and inconvenience of harvesting and transporting marrow from an unrelated donor.

However, there are many unresolved ethical and practical concerns including ownership, consent, use for experimental as well as clinical purposes, ensuring notification of subsequently detected inherited disease, and the need to establish donor banks of sufficient size to give a reasonable chance of obtaining a match for those ethnic groups represented in the population served. At present it is unclear how long cord blood may be safely stored and use has largely been restricted to children because it is generally thought that there are insufficient stem cells in a sample of cord blood to support haematopoiesis in an adult.

A number of public cord-blood banks have been or are in the process of being set up, including five in the UK which together ultimately aim to store 20,000 cord-blood samples. Given that the use of cord blood is currently rare and its therapeutic effect not clear, such banks should be considered experimental and it is essential that the role of cord-blood transplantation is properly evaluated in well-designed prospective studies, preferably RCTs, before such facilities are expanded or cord blood is introduced into clinical practice on an *ad hoc* basis.

Long-term toxicity

Although the use of HDT/PCT has been associated with a number of long-term toxicities, including secondary cancers, infertility and lymphocyte function disorders, there is little comparative data on the incidence of such complications in relation to similar patient populations treated with conventional therapy. Therefore it is unclear to what extent these problems are attributable to HDT/PCT. Long-term follow-up of patients enrolled in RCTs is therefore essential if the question of long-term toxicity is to be addressed adequately. Given that a large proportion of individuals treated with HDT/PCT are likely to be in the younger age groups, this should be given a high priority in trial design.

Conclusions

For all disease sites considered, there is little evidence from randomised studies concerning the effectiveness of HDT/PCT in improving either overall survival or PFS. Reporting of trials has been incomplete and of inconsistent quality, thereby hindering both qualitative and quantitative synthesis. Trials have generally been too small to detect moderate survival benefits reliably and individual publications reporting trials with significant results, positive or negative, must therefore be interpreted cautiously. In light of the constraints of the approach and the data available, quantitative syntheses and combined results presented in this report must also be viewed with caution. On the basis of current published information it is not possible to draw firm conclusions on the role of HDT/PCT in treating any of the malignancies investigated. Although many economic studies have been undertaken, published cost-effectiveness analyses are immature and even the relative costs of HDT/PCT compared with standard treatment are unclear. There also remain important unanswered questions concerning long-term toxicity, and newer techniques and approaches involving purging and the use of cord blood are currently experimental. Further research is undoubtedly required to establish the role of the HDT/PCT approach both for allogeneic and autologous transplantation in the treatment of cancer.

General implications for research

Given the paucity of reliable evidence concerning the use of HDT/PCT, the most important implication for future research is that further evidence from randomised studies is required. New trials must be designed to include sufficient numbers of patients to detect reliably moderate differences in treat-ment effect. For the rarer malignancies this will undoubtedly require international collaboration. In circumstances such as HDT with allogeneic transplantation in leukaemia, where RCTs are unlikely to be possible, it is important that CCTs are appropriately designed and analysed to ensure that like is compared with like. Where allocation is based on donor availability, the appropriate comparison is of those who received a transplant with those who did not for all tissue-typed patients. As HDT/PCT is often used to treat young patients it is important that appropriate comparisons of long-term toxicity and morbidity are undertaken. Ideally this should be done as long-term follow-up on RCTs. Similarly, there is currently little reliable information concerning the costs and cost-effectiveness of HDT/PCT. Given the real or perceived financial burden associated with the widespread use of HDT/PCT it is important that appropriate prospective economic evaluations are undertaken.

General implications for practice

As the potential applications for HDT/PCT widen, it should be appreciated that not all patients are likely to be suitable for such therapy, and for those considered too old or physically unable to tolerate such intensive therapy, conventional interventions are likely to remain the mainstay of treatment.

It is of course impossible to generalise on the current or future role of HDT/PCT across the diverse diseases considered in this report. It is clear that, for historical reasons, HDT/PCT has become established as routine treatment in certain diseases for which conventional therapy offers very little hope of cure (see EBMT survey results, appendix 5). Whilst it is to be hoped that further RCTs will be conducted to establish whether or not this approach is justified, it is clear that in some circumstances the conduct of trials may be difficult. It is important that the same gradual acceptance of HDT/PCT into routine practice by default does not occur for other cancers where currently the approach is experimental. In such circumstances, routine practice should be to consider entering all patients into on-going RCTs.

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References

1. Schmitz N, Gratwohl A, Goldman J, for the Accreditation Sub Committee of the European Group for Blood and Marrow Transplantation (EBMT). Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders. Current practice in Europe in 1996 and proposals for an operational classification. *Bone Marrow Transplant* 1996;**17**:471–7.
2. Gratwohl A, Hermans J. Bone marrow transplantation activity in Europe in 1992; report from the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 1994;**13**:5–10.
3. Gratwohl A, Gorin C, Apperley J, Goldstone A, Rosti G, Bacigalupo A, *et al.* The European Group for Blood and Marrow Transplantation (EBMT); a report from the President and the Chairman of the Working Parties. *Bone Marrow Transplant* 1996;**18**:677–91.
4. Kleignen J, Gøtzsche P, Kunz RA, Oxman AD, Chalmers I. So what's so special about randomisation? In: Maynard A, Chalmers I, editors. Non-random reflections on health services research. London: BMJ Publishing Group; 1997. p. 93–106.
5. Dickersin K, Min Y-I, Meinert CL. Factors influencing publication of research results. *JAMA* 1992;**267**(3):374–8.
6. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.
7. Parmar MKP, Torri V, Stewart LA. Meta-analysis of the published literature for survival endpoints: making a silk purse out of a sow's ear. *Stat Med.* In press 1998.
8. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985;**27**:335–71.
9. Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;**341**:418–22.
10. Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer. Vol 1. Worldwide evidence 1985–1990. Oxford: Oxford University Press; 1990.
11. Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children with lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. Medical Research Council Working Party on Childhood Leukaemia. *Lancet* 1995;**345**:143–8.
12. Uderzo C, Valsecchi MG, Bacigalupo A, Meloni G, Messina C, Polchi P, *et al.* Treatment of childhood acute lymphoblastic leukemia in second remission with allogeneic bone marrow transplantation and chemotherapy: ten-year experience of the Italian Bone Marrow Transplantation Group and the Italian Pediatric Hematology Oncology Association. *J Clin Oncol* 1995;**13**:352–8.
13. Dopfer, R, Henze, G, Bender Gotze C, Ebell, W, Ehninger, G, Friedrich, *et al.* Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM- and CoALL-protocols: results of the German Cooperative Study. *Blood* 1991;**78**:2780–4.
14. Chessells JM, Bailey C, Wheeler K, Richards SM. Bone marrow transplantation for high-risk childhood lymphoblastic leukaemia in first remission: experience in MRC UKALL X. *Lancet* 1992;**340**:565–8.
15. Johnson FL, Thomas ED, Clark BS, Chard RL, Hartmann JR, Storb R. A comparison of marrow transplantation with chemotherapy for children with acute lymphoblastic leukemia in second or subsequent remission. *N Engl J Med* 1981;**305**:846–51.
16. Schaison G, Bordigoni P, Leblanc T, Lamagnere JP, Leverger G, Baruchel A, *et al.* Comparison of bone marrow transplantation (BMT), autologous BMT (ABMT), augmented chemotherapy (AC), in first complete remission in children with very increased risk acute lymphoblastic leukemias (VIRCALL). *Proc Annu Meet Am Soc Clin Oncol* 1993;**12**:A1043.
17. Saarinen UM, Mellander L, Nysom K, Ringden O, Schroeder H, Glomstein A, *et al.* Allogeneic bone marrow transplantation in first remission for children with very high-risk acute lymphoblastic leukemia: a retrospective case-control study in the Nordic countries. Nordic Society for Pediatric Hematology and Oncology (NOPHO). *Bone Marrow Transplant* 1996;**17**:357–63.
18. Borgmann A, Schmid H, Hartmann R, Baumgarten E, Hermann K, Klingebiel T, *et al.* Autologous bone-marrow transplants compared with chemotherapy for children with acute lymphoblastic leukaemia in a second remission: a matched-pair analysis. The Berlin–Frankfurt–Munster Study Group. *Lancet* 1995;**346**:873–6.

19. Boulad F, Steinherz P, Reyes B, Gillio A, Small T, Kernan NA, *et al.* Allogeneic bone marrow transplantation (BMT) vs chemotherapy for the treatment of childhood acute lymphoblastic leukemia (ALL) in second remission (CR2): The MSKCC experience. *Blood* 1994;**84** (10 Suppl 1):251a.

20. Chessells JM, Rogers DW, Leiper AD, Blacklock H, Plowman PN, Richards S, *et al.* Bone-marrow transplantation has a limited role in prolonging second marrow remission in childhood lymphoblastic leukaemia. *Lancet* 1986;**1**:1239–41.

21. Harris R, Feig S, Coccia P, Warkentin P, Wiley F, Lampkin B, *et al.* ALL in second remission – a CCSG study of maintenance chemotherapy vs marrow transplantation. In: Gale R, Champlin R, editors. Progress in Bone Marrow Transplantation. New York: Alan R Liss Inc; 1987. p. 91–5.

22. Torres A, Martinez F, Gomez P, Fornes G, Rojas R, Herrera C, *et al.* Allogeneic bone marrow transplantation versus chemotherapy in the treatment of childhood acute lymphoblastic leukemia in second complete remission. *Bone Marrow Transplant* 1989;**4**:609–12.

23. Ringden O, Bolme P, Lonnqvist B, Gustafsson G, Kreuger A. Allogeneic bone marrow transplantation versus chemotherapy in children with acute leukemia in Sweden. *Pediatr Hematol Oncol* 1989;**6**:137–44.

24. Hoogerbrugge PM, Gerritsen EJ, van der Does–van den Berg A, van der Berg H, Zwinderman AH, Hermans J, *et al.* Case-control analysis of allogeneic bone marrow transplantation versus maintenance chemotherapy for relapsed ALL in children. *Bone Marrow Transplant* 1995;**15**:255–9.

25. Barrett AJ, Horowitz MM, Pollock BH, Zhang MJ, Bortin MM, Buchanan GR, *et al.* Bone marrow transplants from HLA-identical siblings as compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission. *N Engl J Med* 1994;**331**:1253–8.

26. Frassoni F, Bacigalupo A, Van Lint MT, Congiu M, Carekkam A, Martinengo M, *et al.* Bone marrow transplantation versus chemotherapy for patients under 15 years of age in 2nd remission acute lymphoblastic leukaemia (ALL). *Exp Hematol* 1985;**13**(Suppl 17):41.

27. Bacigalupo A, Van Lint MT, Frassoni F, Occhini D, Pittaluga PA, Comelli A, *et al.* Allogeneic bone marrow transplantation versus chemotherapy for childhood acute lymphoblastic leukaemia in second remission. *Bone Marrow Transplant* 1986;**1**:75–80.

28. Wheeler K, Bailey C, Chessells J, Richards S. Comparison of bone marrow transplant and chemotherapy treatment for relapsed childhood acute lymphoblastic leukaemia (ALL). *Exp Hematol* 1996;**24**:A241.

29. Durrant IJ, Richards SM. Results of Medical Research Council trial UKALL IX in acute lymphoblastic leukaemia in adults: report from the Medical Research Council Working Party on Adult Leukaemia. *Br J Haematol* 1993;**85**:84–92.

30. Sebban C, Lepage E, Vernant JP, Gluckman E, Attal M, Reiffers J, *et al.* Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *J Clin Oncol* 1994;**12**:2580–7.

31. Fiere D, Broustet A, Leblond V, Maraninchi D, Castaigne S, Flesch M, *et al.* Comparison of chemotherapy and autologous and allogeneic transplantation as postinduction regimen in adult acute lymphoblastic leukemia: a preliminary multicentric study. *Hamatol Bluttransfus* 1990;**33**:9–12.

32. Bernasconi C, Lazzarino M, Morra E, Alessandrino EP, Pagnucco G, Resegotti L, *et al.* Early intensification followed by ALLO-BMT or AUTO-BMT or a second intensification in adult all: a randomized multicenter study. *Leukemia* 1992;**6**:204–8.

33. Fiere D, Sebban C, Vernant JP, Witz F, Rigal Huguet F, Boucheix C, *et al.* Long term results of chemotherapy, allogeneic or autologous bone marrow transplantation (BMT) as post remission therapy in adult acute lymphoblastic leukemia (ALL) for patients included in a prospective multicentric trial (LALA 87). *Blood* 1994;**84**(10 Suppl 1):251a.

34. Proctor SJ, Hamilton PJ, Taylor P, Carey P, Hargrave S, Evans RG, *et al.* A comparative study of combination chemotherapy versus marrow transplant in first remission in adult acute lymphoblastic leukaemia. *Br J Haematol* 1988;**69**:35–9.

35. Forman SJ, Blume KG. Marrow transplantation versus chemotherapy for adult patients with acute lymphoblastic leukemia: results of a clinical study. *Transplant Proc* 1991;**23**(1 Pt 2):1713–4.

36. Fiere D, Archimbaud E, Extra JM, Marty M, David B, Witz F, *et al.* Calculation of direct standard costs in the evaluation of new technologies: application to the treatment of acute myeloblastic leukemias. *Hamatol Bluttransfus* 1987;**30**:125–9.

37. Mrsic M, Nemet D, Labar B, Bogdanic V, Radman I, Zupancic Salek S, *et al.* Chemotherapy versus allogeneic bone marrow transplantation in adults with acute lymphoblastic leukemia. *Transplant Proc* 1993;**25**(1 Pt 2):1268–70.

38. Mrsic M, Nemet D, Labar B, Bogdanic V, Radman I, Zupancic-Salek S, *et al.* Chemotherapy versus allogeneic bone marrow transplantation in adults with acute lymphoblastic leukaemia. Proceedings of the 18th EBMT Meeting; 31 May–3 June 1992; Stockholm, Sweden. p. 110.

39. Proctor SJ, Taylor PRA, Hamilton PJ. Acute lymphoblastic leukaemia in adults – an unselected, ten year, population based study of 180 cases assessing the role of early transplantation versus standard maintenance in different age cohorts. *Br J Haematol* 1994;**87**:42.

40. Nemet D, Labar B, Bogdanic V, Mrsic M, Skodlar J, Petrovecki M, *et al.* ABMT versus chemotherapy as consolidation of acute leukaemia in first remission – a prospective single-centre study. *Bone Marrow Transplant* 1995;**15**:S55.

41. Diez Martin JL, Queipo de Llano, Llamas P, Regidor C, Cabrera Forés R, *et al.* Treatment of high risk all (HRALL) in 1st CR with autologous bone marrow transplantation (ABMT) or donor bone marrow transplant (BMT) or chemotherapy. A retrospective study. Proceedings of 20th EBMT Meeting; 13–17 March 1994; Harrogate, UK. p. 197.

42. Zander AR, Keating M, Dicke K, Dixon D, Pierce S, Jagannath S, *et al.* A comparison of marrow transplantation with chemotherapy for adults with acute leukemia of poor prognosis in first complete remission. *J Clin Oncol* 1988;**6**:1548–57.

43. Zhang MJ, Hoelzer D, Horowitz MM, Gale RP, Messerer D, Klein JP, *et al.* Long-term follow-up of adults with acute lymphoblastic leukemia in first remission treated with chemotherapy or bone marrow transplantation. The Acute Lymphoblastic Leukemia Working Committee. *Ann Intern Med* 1995;**123**:428–31.

44. Messerer D, Neiss A, Horowitz MM, Hoelzer D, Gale RP. Comparison of chemotherapy and bone marrow transplants using two independent clinical databases. *J Clin Epidemiol* 1994;**47**:1119–26.

45. Messerer D, Neiss A, Aydemir U, Hoelzer D, Arnold R. How can disease-free survival of adult ALL patients with or without transplants be compared? *Onkologie* 1991;**14**:53–5.

46. Tamura S, Takemoto Y, Kanamaru A, Fujiwara H, Miyazaki E, Fujimori Y, *et al.* Comparison of the survivals between bone marrow transplantation and chemotherapy for acute leukemia in first remission – a Japanese single institution study. *Leuk Lymphoma* **8**:361–4.

47. Richards SM, Bailey C, Chessells J, Durrant H, Prentice G. Bone marrow transplant (BMT) for high-risk childhood and adult ALL in first remission compared with chemotherapy. *Proc Eur Haematol Assoc* 1996;**24**:A555.

48. Yoshida T, Harada M, Funada H, Matue G, Shiobara S, Ishino C, *et al.* Allogeneic bone marrow transplantation for the treatment of acute lymphoblastic leukemia. A comparison of bone marrow transplantation with conventional chemotherapy. *Rinsho Ketsueki* 1984;**25**:337–45.

49. Henderson E, Lister T, Greaves M. Leukaemia. 7th ed. Philadelphia: WB Saunders; 1996.

50. National Cancer Institute, Physicians' data query. www/icic.nci.nih.gov/pdq/pdq_dm.htm.

51. Gale RP. The role of bone marrow transplantation in acute myelogenous leukemia. In: Gale R, Champlin R, editors. Progress in bone marrow transplantation. New York: Alan R Liss Inc; 1987. p. 55–75.

52. Amadori S, Testi AM, Arico M, Comelli A, Giuliano M, Madon E, *et al.* Prospective comparative study of bone marrow transplantation and postremission chemotherapy for childhood acute myelogenous leukemia. The Italian Association of Hematology and Pediatric Oncology Cooperative Group. *J Clin Oncol* 1993;**11**:1046–54.

53. Ravindranath Y, Yeager AM, Chang MN, Steuber CP, Krischer J, Graham Pole J, *et al.* Autologous bone marrow transplantation versus intensive consolidation chemotherapy for acute myeloid leukemia in childhood. Pediatric Oncology Group. *N Engl J Med* 1996;**334**:1428–34.

54. Woods WG, Neudorf S, Gold S, Sanders J, Kobrinsky N, Barnard D, *et al.* Aggressive post-remission (REM) chemotherapy is better than autologous bone marrow transplantation (BMT) and allogeneic BMT is superior to both in children with acute myeloid leukemia (AML). *Proc Annu Meeting Am Soc Clin Oncol* 1996;**15**:A1091.

55. Stevens R, Hann I, Wheatley K, Gray R. Improved outcome in pediatric acute myeloid leukemia (AML): results of the United Kingdom Medical Research Council (MRC) AML10 trial. *Proc Annu Meeting Am Soc Clin Oncol* 1995;**14**:1036.

56. Nesbit ME Jr, Buckley JD, Feig SA, Anderson JR, Lampkin B, Bernstein ID, *et al.* Chemotherapy for induction of remission of childhood acute myeloid leukemia followed by marrow transplantation or multiagent chemotherapy: a report from the Children's Cancer Group. *J Clin Oncol* 1994;**12**:127–35.

57. Dahl GV, Kalwinsky DK, Mirro J Jr, Look AT, Pui C H, Murphy SB, *et al.* Allogeneic bone marrow transplantation in a program of intensive sequential chemotherapy for children and young adults with acute nonlymphocytic leukemia in first remission. *J Clin Oncol* 1990;**8**:295–303.

58. Wells RJ, Woods WG, Buckley JD, Odom LF, Benjamin D, Bernstein I, *et al.* Treatment of newly diagnosed children and adolescents with acute myeloid leukemia: a Children's Cancer Group study. *J Clin Oncol* 1994;**12**:2367–77.

59. Michel G, Leverger G, Leblanc T, Nelken B, Baruchel A, Landman Parker J, *et al.* Allogeneic bone marrow transplantation vs aggressive post-remission chemotherapy for children with acute myeloid leukemia in first complete remission. A prospective study from the French Society of Pediatric Hematology and Immunology (SHIP). *Bone Marrow Transplant* 1996;**17**:191–6.

60. Archimbaud E, Thomas X, Michallet M, Jaubert J, Troncy J, Guyotat D, *et al.* Prospective genetically randomized comparison between intensive post-induction chemotherapy and bone marrow transplantation in adults with newly diagnosed acute myeloid leukemia. *J Clin Oncol* 1994;**12**:262–7.

61. Hubner G, Link H, Schonrock Nabulsi P, Wandt H, Gramatzki M, Loffler B, *et al.* Intensive post-remission therapy in acute myeloid leukemia. Results of a prospective comparative study by the South Germany Hemoblastosis Group. *Med Klin* 1996;**91**(Suppl 3):26–32.

62. Reiffers J, Gaspard MH, Maraninchi D, Michallet M, Marit G, Stoppa AM. Comparison of allogeneic or autologous bone marrow transplantation and chemotherapy in patients with acute myeloid leukaemia in first remission: a prospective controlled trial. *Br J Haematol* 1989;**72**:57–63.

63. Zittoun RA, Mandelli F, Willemze R, de Witte T, Labar B, Resegotti L, *et al.* Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *N Engl J Med* 1995;**332**:217–23.

64. Reiffers J, Stoppa AM, Attal M, Michallet M, Marit G, Blaise D, *et al.* Autologous stem cell transplantation versus chemotherapy for adult patients with acute myeloid leukemia in first remission: the BGMT Group experience. *Nouv Rev Fr Hematol* 1993;**35**:17–19.

65. Harousseau JL, Cahn JY, Pignon B, Witz F, Delain M, Lioure B, *et al.* Autologous bone marrow transplantation (ABMT) versus intensive consolidation chemotherapy (ICC) as post remission therapy in adult acute myeloblastic leukemia (AML): final analysis of the GOELAM randomized study. *Proc Annu Meeting Am Soc Clin Oncol* 1996;**15**:A1051.

66. Burnett AK, Goldstone AH, Stevens RF, Hann IM, Rees JK, Wheatley K, *et al.* The role of BMT in addition to intensive chemotherapy in AML in first CR: results of the MRC AML-10 trial. *Blood* 1994;**84**(10 Suppl 1):252a.

67. Reiffers J, Attal M, Michallet M, Marit G, Blaise D, Huguet F, *et al.* Comparison of allogeneic bone marrow transplantation, autologous stem cell transplantation and chemotherapy in patients with acute myeloid leukaemia (AML) in first remission; the BGMT experience. *Bone Marrow Transplant* 1995;**15**(Suppl 1):S54.

68. Conde E, Iriondo A, Rayon C, Richard C, Fanjul E, Garijo J, *et al.* Allogeneic bone marrow transplantation versus intensification chemotherapy for acute myelogenous leukaemia in first remission: a prospective controlled trial. *Br J Haematol* 1988;**68**:219–26.

69. Powles RL, Clink HM, Bandini G, Watson JG, Spence D, Jameson B, *et al.* The place of bone marrow transplantation in acute myelogenous leukaemia. *Lancet* 1980;**1**(8177):1047–50.

70. Appelbaum FR, Fisher LD, Thomas ED. Chemotherapy vs marrow transplantation for adults with acute nonlymphocytic leukemia: a five-year follow-up. *Blood* 1988;**72**:179–84.

71. Champlin RE, Ho WG, Gale RP, Winston D, Selch M, Mitsuyasu R, *et al.* Treatment of acute myelogenous leukemia. A prospective controlled trial of bone marrow transplantation versus consolidation chemotherapy. *Ann Intern Med* 1985;**102**:285–91.

72. Hewlett J, Kopecky KJ, Head D, Eyre HJ, Elias L, Kingsbury L, *et al.* A prospective evaluation of the roles of allogeneic marrow transplantation and low-dose monthly maintenance chemotherapy in the treatment of adult acute myelogenous leukemia (AML): a Southwest Oncology Group study. *Leukemia* 1995;**9**:562–9.

73. Schiller GJ, Nimer SD, Territo MC, Ho WG, Champlin RE, Gajewski JL. Bone marrow transplantation versus high-dose cytarbine based consolidation chemotherapy for acute myelogenous leukemia in first remission. *J Clin Oncol* 1992;**10**:41–6.

74. Labar B, Mrsic M, Bogdanic V, Radman I, Nemet D. Chemotherapy versus bone marrow transplantation in adults with acute myelogenous leukemia. *Exp Hematol* 1991;**19**:A448.

75. Cassileth PA, Harrington DP, Hines JD, Oken MM, Mazza JJ, McGlave P, *et al.* Comparison of post-remission therapies in adult acute myeloid leukemia: preliminary analysis of an ECOG study. Eastern Cooperative Oncology Group. *Hamatol Bluttransfus* 1990;**33**:627–70.

76. Dinsmore R, Shank B, Kapoor N, Teitelbaum HD, Kirkpatrick D, Clarkson B, *et al.* A randomized trial of marrow transplantation (BMT) vs chemotherapy (CT) maintenance for acute myelogenous leukemia in first remission: preliminary results. *Exp Hematol* **15**:215.

77. Gale RP, Horowitz MM, Rees JK, Gray RG, Oken MM, Estey EH, *et al.* Chemotherapy versus transplants for acute myelogenous leukemia in second remission. *Leukemia* 1996;**10**:13–19.

78. Gale RP, Rees JKH, Gray RG, Horowitz MM. Is chemotherapy or transplant better in acute myelogenous leukemia (AML) in second remission? *Exp Hematol* 1991;**19**:572.

79. Sokal JE, Baccarani M. Russo D, Tura, S. Staging and prognosis in chronic myelogenous leukemia. *Semin Haematol* 1988;**25**:49–61.

80. Allan NC, Shepherd PC, Richards SM. Interferon-alpha (IFN-a) prolongs survival for patients with CML in chronic phase: preliminary results of the UK MRC randomized multicenter trial. *Blood* 1994;**84**(10 Suppl 1):382a.

81. Klingebiel T, Creutzig U, Dopfer R, Ehninger G, Schmidt H, Ritter J, *et al.* Bone marrow transplantation in comparison with conventional therapy in children with adult type chronic myelogenous leukemia. *Bone Marrow Transplant* 1990;**5**:317–20.

82. Italian Cooperative Study Group on Chronic Myeloid Leukaemia. Evaluating survival after allogeneic bone marrow transplant for chronic myeloid leukaemia in chronic phase: a comparison of transplant versus no-transplant in a cohort of 258 patients first seen in Italy between 1984 and 1986. Italian Cooperative Study Group on Chronic Myeloid Leukaemia. *Br J Haematol* 1993;**85**:292–9.

83. Hoyle C, Gray R, Goldman J. Autografting in chronic phase CML using unmanipulated PBSCs long term follow up. Proceedings of the 19th EBMT Meeting; 17–21 January 1993; Garmisch-Partenkirchen, Germany. p. 304.

84. Gale RP, Hehlmann R, Horowitz MM, Ansari H, Hochhaus A, Zhang MJ. Therapy of chronic phase CML: comparison of hydroxyurea, interferon and HLA-identical sibling transplants. *Blood* 1994;**84**(10 Suppl 1):538a.

85a. Longo DL. What's the deal with follicular lymphomas? *J Clin Oncol* 1993;**11**:202–8.

85b. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, *et al.* Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphomas. *N Engl J Med* 1993;**328**:1002–6.

86a. Velasquez WS, Hagemeister F, McLaughlin P. E-SHAP: an effective treatment for refractory and relapsing lymphoma: a long follow-up. *Proc Annu Meeting Am Soc Clin Oncol* 1992;**11**:326.

86b. The International NHL prognostic factors project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993;**329**:987–94.

87. Gianni AM, Bregni M, Siena S, Brambilla C, Di Nicola M, Lombardi F, *et al.* High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med* 1997;**336**:1290–7.

88. Santini G, Salvagno LT, Chisesi T, Leoni P, Oliviell A, Congiu M, *et al.* VACOP-B vs VACOP-B + autologous BM transplantation (ABMT) for aggressive non-Hodgkin's lymphoma. A study of the non-Hodgkin's Lymphoma Cooperative Study Group (NHLSCG). *Bone Marrow Transplant* 1997;**18**(Suppl 1):613.

89. Gisselbrecht C, Lepage E, Morel P, Lederlin P, Coiffier B, Tilly H, *et al.* Short and intensified treatment with autologous stem cell transplantation (ASCT) versus ACVB regimen in poor prognosis aggressive lymphoma LNH93-3 protocol. *Bone Marrow Transplant* 1996;**19**(Suppl 1):S153.

90. Haioun C, Lepage E, Gisselbrecht C, Bastion Y, Coiffier B, Bosly A, *et al.* Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87 2. *J Clin Oncol* 1997;**15**:1131–7.

91. Martelli M, Vignetti M, Zinzani PL, Gherlinzoni F, Meloni G, Fiacchini M, *et al.* High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: a prospective randomized Italian multicenter study. *J Clin Oncol* 1996;**14**:534–42.

92. Verdonck LF, van Putten WL, Hagenbeek A, Schouten HC, Sonneveld P, van Imhoff GW, *et al.* Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1995;**332**:1045–51.

93. Philip T, Guglielmi C, Hagenbeek A, Somers R, van der Lelie H, Bron D, *et al.* Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995;**333**:1540–5.

94. Philip T, Gomez G, Chauvin F. Autologous bone marrow transplantation in relapsed non Hodgkin's lymphoma. *N Engl J Med* 1996;**334**:991.

95. Da WM, Huang YS, Zhong JT, Liu Y, Ou YX. Comparison of treatment for patients with malignant lymphoma receiving autologous bone marrow transplantation and chemotherapy. *Exp Hematol* 1994;**22**:735.

96. Morel P, Laporte JP, Fouillard L, Noel MP, Lesage S, Detourmignies L, *et al.* Autologous bone marrow transplantation (ABMT) as consolidation therapy may prolong remission in newly diagnosed high-risk follicular lymphoma (FL). A pilot study of 34 cases. *Br J Haematol* 1994;**87**:229.

97. Pettengell R, Radford JA, Morgenstern GR, Scarffe JH, Harris M, Woll PJ, *et al.* Survival benefit from high-dose therapy with autologous blood progenitor-cell transplantation in poor-prognosis non-Hodgkin's lymphoma. *J Clin Oncol* 1996;**14**:586–92.

98. Canellos GP, Anderson JR, Propert KJ. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD or MOPP alternating with ABVE. *N Engl J Med* 1992;**327**:1478–84.

99. Longo D, Young RC, Wesley M. 20 Years of MOPP therapy for Hodgkin's disease. *J Clin Oncol* 1986;**4**:1295–1306.

100. Longo DL, Duffey PL, Young RC. Conventional dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol* 1992;**10**:210–18.

101. Hasenclever D, Diehl V. A numerical index to predict tumour control in advanced Hodgkin's disease. *Blood* 1996;**88**:673a.

102. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, *et al.* Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993;**341**:1051–4.

103. Carella AM, Carlier P, Congiu A, Occhini D, Nati S, Santini G, *et al.* Autologous bone marrow transplantation as adjuvant treatment for high-risk Hodgkin's disease in first complete remission after MOPP/ABVD protocol. *Bone Marrow Transplant* 1991;**8**:99–103.

104. Moreau P, Milipied N, Andrieu JM, Jais JP, Harousseau JL. Comparison of combined chemotherapy (CT)-radiotherapy (RT) and early stem cell transplantation (ASCT) in advanced Hodgkin's Disease (HD). *Bone Marrow Transplant* 1995;**15**(Suppl 2):S162.

105. Cooper MR, McIntyre OR, Propert KJ, Kochwa S, Anderson K, Coleman M, *et al.* Single, sequential and multiple alkylating agent therapy for multiple myeloma: a CALGB study. *J Clin Oncol* 1996;**4**:1331–9.

106. Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. *J Clin Oncol* 1992;**10**:178–9.

107. Barlogie B, Jagannath S, Vesole DH, Naucke S, Cheson B, Mattox S, *et al.* Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 1997;**89**:789–93.

108. MacLennan IC, Chapman C, Dunn J, Kelly K. Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. The Medical Research Council Working Party for Leukaemia in Adults. *Lancet* 1992;**339**:200–5.

109. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet G, Rossi JF, *et al.* High dose therapy in multiple myeloma: a prospective randomized study of the 'Intergroup Francais du Myelome' (IFM). *Blood* 1994;**84**(10 Suppl 1):386a.

110. Fermand JP, Ravaud P, Chevret S, Leblond V, Divine M, Dreyfus F, *et al.* High-dose therapy and autologous blood stem cell transplantation in multiple myeloma: preliminary results of a randomized trial involving 167 patients. *Stem Cells* 1995;**13**(Suppl 2):156–9.

111. Bjorkstrand BB, Ljungman P, Svensson H, Hermans J, Alegre A, Apperley J, *et al.* Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood* 1996;**88**:4711–78.

112. Alexanian R, Dimopoulos MA, Delasalle KB, Hester J, Champlin R. Myeloablative therapy for primary resistant multiple myeloma. *Stem Cells* 1995;**13**(Suppl 2):118–21.

113. Henon P, Donatini B, Eisenmann JC, Becker M, Beck Wirth G. Comparative survival, quality of life and cost-effectiveness of intensive therapy with autologous blood cell transplantation or conventional chemotherapy in multiple myeloma. *Bone Marrow Transplant* 1995;**16**:19–25.

114. Gianni AM, Tarella C, Bregni M, Siena S, Lombardi F, Gandola L, *et al.* High-dose sequential chemoradiotherapy, a widely applicable regimen, confers survival benefit to patients with high-risk multiple myeloma. *J Clin Oncol* 1994;**12**:503–9.

115. Cassini M, Mitterer M, Hirber J, Amaddii G, Fabris P, Prinoth O, *et al.* Improvement of overall survival and quality of life in multiple myeloma with adverse prognostic factors after high-dose therapy and autologous blood progenitor support. Proceedings of the 19th EBMT Meeting; 17–21 January 1993; Garmisch-Partenkirchen, Germany. S69.

116. Crowley J, Jagannath S, Salmon S, Vesole DH, Tricot G, Barlogie B. Standard VAD (SWOG 8624) versus total therapy (TT) with 2 autotransplants (AT) for untreated multiple myeloma (MM). *Proc Annu Meeting Am Soc Clin Oncol* 1994;**13**:A1401.

117. Cancer Research Campaign. Fact Sheet 6.1. Breast Cancer – UK. 1996.

118. Antman KH, Rowlings PA, Vaughan WP, Pelz CH, Fay JW, Fields KK, *et al.* High-dose chemotherapy with autologous haematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol* 1997;**15**:1870–9.

119. Greenberg PAC, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Budzar AU. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996;**14**:2197–205.

120. Early Breast Cancer Trialists' Collaborative Group. Systematic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomised trials, involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992;**339**:71–85.

121. Bezwoda WR, Seymour L, Dansey RD. High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. *J Clin Oncol* 1995;**13**:2483–9.

122. Ljungman P, Bjorkstrand B, Gahrton G, Nordenstrom J, Shanwell A, Glas U, *et al.* High-dose chemotherapy in breast cancer. Promising results in combination with stem cell support. *Lakartidningen* 1995;**92**:851–3.

123. Peters WP, Jones RB, Vredenburgh J, Shpall EJ, Hussein A, Elkordy M, *et al.* A large, prospective, randomized trial of high-dose combination alkylating agents (CPB) with autologous cellular support (ABMS) as consolidation for patients with metastatic breast cancer achieving complete remission after intensive doxorubicin-based induction therapy (AFM). *Proc Annu Meeting Am Soc Clin Oncol* 1996;**15**:A149.

124. Health Technology Assessment Information Service (ECRI). High-dose chemotherapy with autologous bone marrow transplantation and/or blood cell transplantation for the treatment of metastatic breast cancer.

125. Peters WP, Ross M, Vredenburgh J, Meisenberg B, Marks LB, Winer E, *et al.* High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 1993;**11**:1132–43.

126. Peters WP, Berry D, Vredenburgh JJ, Hussein A, Rubin P, Elkordy M, *et al.* Five year follow-up of high-dose combination alkylating agents with ABMT as consolidation after standard-dose CAF for primary breast cancer involving greater than or equal to 10 axillary lymph nodes (Duke/CALGB 8782). *Proc Annu Meeting Am Soc Clin Oncol* 1995;**14**:A933.

127. Huelskamp AM, Abeloff MD, Armstrong DK, Fetting JH, Gordon G, Davidson NE, *et al.* High-dose consolidation chemotherapy for stage IIIB breast cancer in remission: intermediate follow-up and comparison with intensively treated historical controls. *Proc Annu Meeting Am Soc Clin Oncol* 1995;**14**:A933.

128. Gianni AM, Siena S, Bregni M, Di Nicola M, Dodero A, Zambetti M, *et al.* 5-Year results of high-dose sequential (HDS) adjuvant chemotherapy in breast cancer with greater than or equal to 10 positive nodes. *Proc Annu Meet Am Soc Clin Oncol* 1995:**14**:A61.

129. de Vries EGE, ten Vergert EM, Mastenbroek CG, Dalesio O, Rohenhuis S. Breast cancer studies in The Netherlands. *Lancet* 1996;**348**:407–9.

130. Rutqvist LE. Randomized adjuvant breast cancer trials in Sweden. *Cancer* 1994;**74**:1135–8.

131. International Germ Cell Cancer Collaborative Group. International germ cell consensus classification: a prognostic factor based staging system for metastatic germ cell cancers. *J Clin Oncol* 1997;**15**:594–603.

132. Gerl A, Clemm C, Schmeller N. Prognosis after salvage treatment for unselected male patients. *Br J Cancer* 1995;**72**:1026–32.

133. Chevreau C, Droz JP, Pico JL, Biron P, Kerbrat P, Cure H, *et al.* Early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor risk non-seminomatous germ cell tumours. Preliminary results of a French randomized trial. *Eur Urol* 1993;**23**:213–7.

134. Bokemeyer C, Harstrick A, Ruther U, Metzner B, Arseniev L, Kadar J, *et al.* Sequential treatment with high-dose VIP-chemotherapy plus peripheral blood stem cell (PBSC) support in advanced germ cell cancer. *Proc Annu Meet Am Soc Clin Oncol* 1995;**14**:A596.

135. Parkin DM, Sax AL. Lung cancer: worldwide variation in occurrence and proportion attributable to tobacco use. *Lung Cancer* 1993;**9**:1–16.

136. Rankin EM. Non-small cell lung cancer. In: Slevin ML, Staquet MJ, editors. Randomised trials in cancer: a critical review. New York: Raven Press; 1986. p. 447–92.

137. Souhami RL, Law K. Longevity in small cell lung cancer. *Br J Cancer* 1990;**61**:584–9.

138. Humblet Y, Symann M, Bosly A, Delaunois L, Francis C, Machiels J, *et al.* Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: a randomized study. *J Clin Oncol* 1987;**5**:1864–73.

139. Souhami RL, Hajichristou HT, Miles DW, Earl HM, Harper PG, Ash CM, *et al.* Intensive chemotherapy with autologous bone marrow transplantation for small-cell lung cancer. *Cancer Chemother Pharmacol* 1989;**24**:321–5.

140. Advanced Ovarian Cancer Trialists Group. Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials. *BMJ* 1991;**303**:884–93.

141. Advanced Ovarian Cancer Trialists Group. Chemotherapy in advanced ovarian cancer: five year update of 4 systematic meta-analyses of individual patient data from 37 randomised controlled trials. *Br J Cancer.* In press 1998.

142. Thigpen JT. Dose-intensity in ovarian carcinoma: hold, enough? *J Clin Oncol* 1997;**15**:1291–3.

143. Dufoir T, Saux MC, Terraza B, Marit G, Guessard S, Foulon G, *et al.* Comparative cost of allogeneic or autologous bone marrow transplantation and chemotherapy in patients with acute myeloid leukaemia in first remission. *Bone Marrow Transplant* 1992;**10**:323–9.

144. Aulesa C, Olive T, Bastida P, Ortega JJ. Cost assessment of two treatment modalities for acute non lymphoblastic leukaemia in children: prolonged sequential polychemotherapy versus short intensification chemotherapy followed by allogeneic or autologous bone marrow transplant. *Biol Clin Hematol* 1992;**14**:221–8.

145. Welch HG, Larson EB. Cost effectiveness of bone marrow transplantation in acute nonlymphocytic leukemia. *N Engl J Med* 1989;**321**:807–12.

146. Corker RL. The cost-effectiveness of bone marrow transplantation relative to consolidation chemotherapy for acute myelogenous leukemia patients in first remission. *Diss Abstr Int (B)* 1989;**50**:515.

147. Uyl-de Groot CA, Hagenbeek A, Verdonck LF, Lowenberg B, Rutten FF. Cost-effectiveness of ABMT in comparison with CHOP chemotherapy in patients with intermediate- and high-grade malignant non-Hodgkin's lymphoma (NHL). *Bone Marrow Transplant* 1995;**16**:463–70.

148. Barr R, Furlong W, Henwood J, Feeny D, Wegener J, Walker I, *et al.* Economic evaluation of allogeneic bone marrow transplantation: a rudimentary model to generate estimates for the timely formulation of clinical policy. *J Clin Oncol* 1996;**14**:1413–20.

149. Masaoka T. Medical cost of acute leukemia treatment bone marrow transplantation and chemotherapy. *Exp Hematol* 1994;**22**:680.

150. Viens-Bitker C, Blum C, Bessis M, Cordonnier C, Rochant H, Jolly D. Calculation of direct standard costs in the evaluation of new technologies: application to the treatment of acute myeloblastic leukemias. *Rev Epidemiol Sante Publique* 1986;**34**:41–51.

151. Rollinson DH. The cost of marrow transplantation compared with cost of conventional treatment for acute leukaemia and aplastic anaemia. *NZ Med J* 1982;**95**:310–11.

152. Kay HE, Lawler SD, Powles RL, Clink HM. Cost of bone-marrow transplants in acute myeloid leukaemia. *Lancet* 1980;**1**:1067–9.

153. Armitage JO, Klassen LW, Burns CP, Kugler JW, Ray TL, Gingrich RD, *et al.* A comparison of bone marrow transplantation with maintenance chemotherapy for patients with acute nonlymphoblastic leukemia in first complete remission. *J Clin Oncol* 1984;**7**:273–8.

154. Zaidi Y, Clarke C, Hutchinson RM. CHOP/ABMT is less cost effective than CHOP alone in intermediate and high grade malignant non-Hodgkin's lymphoma. *Bone Marrow Transplant* 1996; **17**(Suppl 1):46.

155. Desch CE, Lasala MR, Smith TJ, Hillner BE. The optimal timing of autologous bone marrow transplantation in Hodgkin's disease patients after a chemotherapy relapse. *J Clin Oncol* 1992;**10**:200–9.

156. Hillner BE, Smith TJ, Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results. *JAMA* 1992;**267**:2055–61.

157. Le Corroller AG, Faucher C, Auperin A, Blaise D, Fortanier C, Benhamou E, *et al.* Autologous peripheral blood progenitor-cell transplantation versus autologous bone marrow transplantation for adults and children with non-leukaemic malignant disease. *Pharmocoeconomics* 1997;**11**:454–463.

158. Smith TJ, Hillner BE, Schmitz N, Linch DC, Dreger P, Goldstone AH, *et al.* Economic analysis of a randomized clinical trial to compare filgrastim-mobilized peripheral-blood progenitor-cell transplantation and autologous bone marrow transplantation in patients with Hodgkin's and non-Hodgkin's lymphoma. *J Clin Oncol* 1997;**15**:5–10.

159. Henon P, Donatini B, Eisenmann JC, Becker M, Beck Wirth G. Comparative survival, quality of life and cost-effectiveness of intensive therapy with autologous blood cell transplantation or conventional chemotherapy in multiple myeloma. *Bone Marrow Transplant* 1995;**16**:19–25.

160. Hartmann O, le Corroller AG, Blaise D, Michon J, Phillip I, Norol F, *et al.* Peripheral blood stem cell and bone marrow transplantation for solid tumors and lymphomas: hematologic recovery and costs. *Ann Intern Med* 1997;**126**:600–7.

161. Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA, Ferrant A, *et al.* Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. *Lancet* 1996;**347**:353–7.

162. Russell NH, Pacey S. Economic evaluation of peripheral blood stem cell transplantation for lymphoma. *Lancet* 1992;**340**:1290.

163. Duncan N, Hewetson M, Powles R, Raje N, Mehta J. An economic evaluation of peripheral blood stem cell transplantation as an alternative to autologous bone marrow transplantation in multiple myeloma. *Bone Marrow Transplant* 1996;**18**:1175–8.

164. Faucher C, le Corroller AG, Blaise D, Novakovitch G, Manonni P, Moatti JP, *et al.* Comparison of G-CSF-primed peripheral blood progenitor cells and bone marrow auto transplantation: clinical assessment and cost-effectiveness. *Bone Marrow Transplant* 1994;**14**:895–901.

165. Knechtli CLC, Lumley MA, Baker PJ, Milligan DW. PBSC transplantation versus bone marrow autografting: a cost benefit analysis. *Br J Haematol* 1994;**87**(Suppl 1):37.

166. Ager S, Scott MA, Mahendra P, Richards EM, Jestice HK, Boraks P, *et al.* Peripheral blood stem cell transplantation after high-dose therapy in patients with malignant lymphoma: a retrospective comparison with autologous bone marrow transplantation. *Bone Marrow Transplant* 1995;**16**:79–83.

167. de Arriba F, Heras I, del Carmen Garcia M, Moraleda JM, Funes C, Ferrer F, *et al.* Coste economico del autotrasplante de progenitores hematopoyeticos. *Med (Clin) Barc* 1996;**106**:329–32.

168. Faucher C, le Corroller AG, Macquart-Moulin G, Auquier P, Chabannon C, Viens P, *et al.* Autologous bone marrow transplantation vs peripheral blood progenitor cells (PBPC) transplantation for poor risk breast cancer: clinical, economic and quality of life assessment. *Bone Marrow Transplant* 1995;**15**(Suppl 2):S110.

169. Rio B, Marjanovic Z, Belhocine R, Vekhoff A, Andrieu V, Klaren J, *et al.* Difference in costs for autologous transplantations with either peripheral blood or bone marrow stem-cells. A retrospective analysis of transplantations for lymphoma, Hodgkin disease and myeloma during one year in a single center. *Ann Med Interne (Paris)* 1996;**147**:313–9.

170. Shore T, Woloschuk D, Painter V, Bonnar L, Rubinger M, Schroeder M, *et al.* Peripheral blood progenitor cell transplants (PBPCT) do provide cost savings in the Canadian health care system. *Proc Annu Meeting Am Soc Clin Oncol* 1996;**15**:A1010.

171. Julia A, Bueno J, Gadea N, Massuet L, del Bano C. Estudio economico del coste del autotrasplante de precursores hematopoyeticos de sangre periferica comparado con el de medula osea. *Med Clin (Barc)* 1995;**105**:131–5.

172. Uyl-de Groot CA, Richel DJ Rutten FF. Peripheral blood progenitor cell transplantation mobilised by r-metHuG-CSF (filgrastim); a less costly alternative to autologous bone marrow transplantation. *Eur J Cancer* 1994;**30A**:1631–5.

173. Uyl-de Groot CA, Ossenkoppele GJ, van Riet AA, Rutten FF. The costs of peripheral blood progenitor cell reinfusion mobilised by granulocyte colony-stimulating factor following high dose melphalan as compared with conventional therapy in multiple myeloma. *Eur J Cancer* 1994;**30A**:457–9.

174. Beyer J, Schewlla N, Zingsem J, Strohsheer I, Schwaner I, Oettle H, *et al.* Hematopoietic rescue after high-dose chemotherapy using autologous peripheral blood progenitor cells or bone marrow: a randomized comparison. *J Clin Oncol* 1995;**13**:1328–35.

175. Weisdorf DJ, Verfaillie CM, Miller WJ, Blazar BR, Perry E, Shu XO, *et al.* Autologous bone marrow versus non-mobilized peripheral blood stem cell transplantation for lymphoid malignancies: a prospective comparative trial. *Am J Hematol* 1997;**54**:202–8.

176. Janssen WE, Smilee RC, Elfenbein GJ. A prospective randomized trial comparing blood- and marrow-derived stem cells or hematopoietic replacement following high-dose chemotherapy. *Journal of Hematotherapy* 1995;**4**:139–40.

177. Stone RM, Neuberg D, Soiffer R, Takvorian T, Whelan M, Rabinowe SN, *et al.* Myelodysplastic syndrome as a late complication following autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol* 1994;**12**:2535–42.

178. Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, Weisdorf DJ. Myelodysplastic syndrome after autologous bone marrow transplantation: an additional late complication of curative cancer therapy. *Blood* 1994;**83**:3780–6.

179. Witherspoon RP, Fisher LD, Schoch G, Martin P, Sullivan KM, Sanders J, *et al.* Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. *N Engl J Med* 1989;**321**:784–9.

180. Pedrazzini A, Freedman AS, Anderson J. Anti-B cell monoclonal antibody purged autologous bone marrow transplantation for B-cell non-Hodgkin's lymphoma: phenotypic reconstitution and B-cell function. *Blood* 1989;**74**:2203–11.

181. Soiffer RJ, Bosseman L, Murray C, Cochran K, Daley J, Ritz J. Reconstitution of T-cell function after CD6 depleted allogeneic bone marrow transplantation. *Blood* 1990;**75**:2076–84.

182. Wingard JR, Curbow B, Baker F. Health, functional status and employment of adult survivors of bone marrow transplantation. *Ann Intern Med* 1991;**114**:113–8.

183. Mumma GH, Mashberg D, Lesko LM. Long-term psychosexual adjustment of acute leukemia survivors: impact of marrow transplantation versus conventional chemotherapy. *Gen Hosp Psychiatry* 1992;**14**:43–55.

184. Molassiotis A, van den Akker OBA, Milligan DW, Boughton BJ, Holmes JA, Thomas S. Quality of life in long-term survivors of marrow transplantation: comparison with a matched group receiving maintenance chemotherapy. *Bone Marrow Transplant* 1996;**17**:249–58.

185. Mashberg DE. Psychological adjustment of patients with chronic leukaemia. *Diss Abstr Int (B)* 1989;**50**:2629.

186. Gluckman E, Broxmeyer HE, Auerbach AD, Friedman H, Douglas GW, Devergie A, *et al.* Hematopoietic reconstitution in a patient with Fanconi's anaemia by means of umbilical cord blood from an HLA-identical sibling. *N Engl J Med* 1989;**321**:1174–6.

187. Vilmer E, Sterkers G, Rahimy C, Denamur E, Elion J, Broyart A, *et al.* HLA-mismatched cord-blood transplantation in a patient with advanced leukemia. *Transplantation* 1992;**53**:1155–7.

188. Pahwa RN, Fleischer A, Shih S, Uckan D, Durham S, Garofalo P, *et al.* Erythrocyte-depleted allogeneic human umbilical cord blood transplantation. *Blood Cells* 1994;**20**:267–74.

189. Miniero R, Busca A, Roncarolo MG, Saitta M, Iavarone A, Timeus F, *et al.* HLA-haploidentical umbilical cord blood stem cell transplantation in a child with advanced leukemia: clinical outcome and analysis of hematopoietic recovery. *Bone Marrow Transplant* 1995;**16**:229–40.

190. Locatelli F, Maccario R, Comoli P. Haematopoietic and immune recovery after transplantation of cord blood progenitor cells in children. *Bone Marrow Transplant* 1996;**18**:1095–101.

191. Wagner JE, Broxmeyer HE, Byrd RL, Zehnbauer B, Schmeckpeper B, Shah N, *et al.* Transplantation of umbilical cord blood after myeloablative therapy: analysis of engraftment. *Blood* 1992;**79**:1874–81.

192. Bogdanic V, Nemet D, Kastelan A, Latin V, Petrovecki M, Brkljacic Surlakovic L, *et al.* Umbilical cord blood transplantation in a patient with Philadelphia chromosome-positive chronic myeloid leukemia. *Transplantation* 1993;**56**:477–9.

193. Mrsic M, Nemet D, Labar B, Bogdanic V, Radman I, Zupancic-Salek S, *et al.* Chemotherapy versus allogeneic bone marrow transplantation in adults with acute lymphoblastic leukaemia. Proceedings of the 18th EBMT Meeting; 31 May–3 June 1992; Stockholm, Sweden. p. 110.

194. Fernandez MN, Regidor C, Diez JL, Fores R, Sanjuan I, Briz M, *et al.* HLA haploidentical cord blood cell transplant in a 15-year-old, 50 kg weight patient: successful treatment for chronic myeloid leukemia after myeloid blastic transformation. *Bone Marrow Transplant* 1996;**17**:1175–8.

195. Abecasis MM, Machado AM, Boavida G, Silva MG, Lucio P, Ambrosio, A, *et al.* Haploidentical cord blood transplant contaminated with maternal T cells in a patient with advanced leukaemia. *Bone Marrow Transplant* 1996;**17**:891–5.

196. Brichard B, Vermylen C, Ninane J, Cornu G, Deneys V, De Bruyere M. Transplantation of umbilical cord blood in a refractory lymphoma. *Pediatr Hematol Oncol* 1995;**12**:79–81.

197. Ohnuma K, Toyoda Y, Nishihira H, Iguchi A, Honda K, Nagao T, *et al.* Successful engraftment of sibling cord-blood stem cell transplantation in a child with acute promyelocytic leukemia. *Int J Hematol* 1996;**64**:271–8.

198. Wagner JE, Kernan NA, Steinbuch M, Broxmeyer HE, Gluckman E. Allogeneic sibling umbilical-cord-blood transplantation in children with malignant and non-malignant disease. *Lancet* 1995;**346**:214–9.

199. Kurtzberg J, Graham M, Casey J, Olson J, Stevens CE, Rubinstein P. The use of umbilical cord blood in mismatched related and unrelated hemopoietic stem cell transplantation. *Blood Cells* 1994;**20**:275–83.

200. Sweetman R, Rosenthal J, Sender LS, Cairo MS. Unrelated cord blood as a source of stem cells in children and adults undergoing myeloablative therapy for malignant and non-malignant conditions. *Proc Annu Meet Am Soc Clin Oncol* 1996;**15**:A10.

201. Lambertenghi Deliliers G, Soligo D, Della Volpe A, Bertolini F, Poli F, Romitti L, *et al.* Unrelated mismatched cord blood transplantation in an adult with secondary AML. *Bone Marrow Transplant* 1996;**18**:469–72.

202. Guimaraes A, Machado A, Bertolini F, Lecchi L, Sirchia G, Abecasis M. Bone marrow transplantation for an adult with CML in chronic phase using unrelated cord blood, a case report. *Eur J Haematol* 1996:**24**:A939.

203. Gorin NC, Laporte JPH, Rubinstein P, Najman A. Successful unrelated mismatched cord blood transplant with minimal cell dose and cytokine combination in an adult patient with chronic myelocytic leukemia (CML). *Exp Hematol* 1996;**25**:1139.

204. Laporte JP, Gorin NC, Rubinstein P, Lesage S, Portnoi MF, Barbu V, *et al.* Cord-blood transplantation from an unrelated donor in an adult with chronic myelogenous leukemia. *N Engl J Med* 1996;**335**:167–70.

205. Wagner JE, Rosenthal J, Sweetman R, Shu XO, Davies SM, Ramsay NK, *et al.* Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. *Blood* 1996;**88**:795–802.

206. Kurtzberg J, Laughlin M, Michael LG, Smith C, Olson J, Halperin EC, *et al.* Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *N Engl J Med* 1996;**335**:157–66.

207. Beguin Y, Comu G, Brichard B, Debruyn C, De Bruyere M, De Hemptinne D, *et al.* Hematological results and practical issues of the Belgian cord blood banking project. *Bone Marrow Transplant* 1996;**1**(Suppl 1):632.

208. Fisher CA. Establishment of cord blood banks for use in stem cell transplantation: commentary. *Curr Probl Obstet Gynecol Fertil* 1996;**March/April**:55–58.

209. Technologica. Blue Cross and Blue Shield Association. www.bluecares.com/tecnologia/tecumbilical.html

Appendix 1

Systematic review protocol

Introduction

The principal dose-limiting effect of most chemotherapy agents is bone marrow suppression. In order to circumvent this and allow administration of higher, potentially more effective doses, several strategies are available. All provide a means of reconstituting the bone marrow after treatment with cells that have not been exposed to the chemotherapeutic agents. Reconstitution may be from harvested bone marrow or peripheral blood progenitors ('stem-cells'). Autologous rescue employs a patient's own progenitors whilst allogeneic transplantation involves the use of progenitors derived from a different person. Allogeneic transplantation may have a therapeutic effect beyond that of the cytotoxic drugs in that the transplanted cells may exert an immunologic effect upon the malignancy, but the main principle underlying high-dose therapy (HDT) is that more intensive treatment should yield better results by killing more malignant cells.

Initially, HDT was restricted to 'salvage' treatment of patients in whom conventional treatment failed to eradicate disease. However, with the advent of improved supportive measures, particularly the use of peripheral blood progenitor cell rescue, the toxicity and mortality from high-dose treatment has fallen substantially. This in turn has led to a widening of its use.

HDT with autologous stem-cell transplantation is now becoming widely applied to allow dose intensification. Until recently, its use was confined to haematological malignancies, but in the last 5 years there has been a marked increase in use for solid tumours. This is particularly true of breast cancer, which is now the commonest setting for this form of treatment in the USA.

Sibling allogeneic transplantation is a well established treatment and is regularly used for the management of haematopoietic malignancies. Transplantations with progenitor cells from unrelated donors, however, are associated with a high mortality and morbidity and to date their use is largely experimental.

An increased understanding of the mechanism and control of graft versus host disease is necessary before the treatment could be used routinely to treat some of the many potential recipients for whom a sibling allograft is unavailable.

As the indications for HDT broaden and new technologies which may improve the effectiveness of the treatment are developed, so the numbers of patients treated increase. Despite several thousand papers and abstracts reporting on the results of transplant series there is still great uncertainty as to the true effectiveness of this treatment modality.

It is therefore both necessary and timely to undertake a systematic review to evaluate the evidence currently available in the literature concerning the use of HDT. This review therefore aims to identify all relevant published studies of HDT. The methods described in this protocol will be used to appraise systematically the available evidence and to provide an objective and reliable summary of that evidence.

The best evidence of the effectiveness of any healthcare intervention comes from the results of well-conducted randomised controlled trials (RCTs). The potential biases associated with non-randomised studies are well known. For this reason, although this review will identify all studies, it will place most emphasis on the results of RCTs. Where possible the results of RCTs will be combined quantitatively, as will those of controlled clinical trials (CCTs). Where insufficient randomised/controlled data is available, other comparative studies will be summarised and appraised qualitatively. The decision as to whether other comparative studies will be appraised will be taken when the number of RCTs and CCTs, the total number of patients entered and the number of events are known, but before any analysis of data has been performed. No summation of data from non-RCTs/CCTs will be performed.

Aims

The purpose of this review is to identify all studies investigating the effectiveness, in terms of survival and/or progression-free survival, of HDT combined with progenitor cell transplantation. The literature will be assessed in several key areas, both

to synthesise current evidence for the use of HDT and to identify research questions to be addressed in the future.

The review will concentrate on malignancies which were identified as diseases in which a large proportion of the current transplants are performed. For completeness a literature search for randomised and controlled clinical trials will be carried out to identify any area in which a large number of Phase III trials into the efficacy of BMT may have been carried out. If such an area exists, it will be included in the review.

Primary questions to be addressed

1. Does HDT improve survival/progression-free survival when compared to conventional therapy in
   - breast cancer
   - acute and chronic leukaemia
   - malignant lymphoma
   - multiple myeloma
   - ovarian cancer
   - testicular cancer
2. What evidence is there concerning the cost-effectiveness of HDT?
3. What evidence is there comparing the long term toxicities of HDT with those of conventional chemotherapy?
4. What evidence is there concerning the use of cord-blood transplantation?

Additional questions to be addressed

1. What randomised evidence is there comparing peripheral stem-cell with autologous bone marrow transplantation?
2. What randomised evidence is there comparing purged and unpurged transplantation?

Methods

Literature search strategy

All papers indexed on the bibliographic databases listed below up to and including 1 November 1996 will be searched using the Knight-Ridder Probase software. An updated search will be performed to identify RCTs and CCTs that appear on the databases up to and including 31 January 1997.

- Medline
- Embase
- CancerLit
- Science Citation Index
- Biosis
- The Cochrane Controlled Trials Register
- NHS Economic Evaluation Database

Given the emphasis that will be placed on the results of RCTs, trial registers will be searched for both ongoing and closed trials which may remain unpublished. The following registers will be searched up to and including 31 January 1997.

- PDQ (Open Trials)
- PDQ (Closed Trials)
- UKCCCR Trials Register
- Center Watch Clinical Trials Listings

References obtained from various sources will be managed using the Procite bibliographic package.

The results of all literature searches will be archived to floppy disk.

Handsearching

The following journals were listed by the clinical coordinators as those thought likely to include relevant publications: *Acta Hematologia, American Journal of Hematology, American Journal of Medicine, Annals of Haematology, Annals of Internal Medicine, Annals of Oncology, Blood, Blood Cells Molecules and Disease, Molecules and Diseases, Bone Marrow Transplantation, British Journal of Cancer, British Journal of Haematology, British Medical Journal, Cancer, Cancer Research, European Journal of Cancer, European Journal of Hematology, Experimental Hematology, Hematological Oncology, Journal of Clinical Investigation, Journal of Hematotherapy, Journal of the National Cancer Institute, Journal of Clinical Oncology, Journal of the American Medical Association, Lancet, Leukemia, Leukemia and Lymphoma, New England Journal of Medicine, Seminars in Hematology, Seminars in Oncology, Transplantation*.

However, all of these journals are indexed on one or more of the electronic databases being searched and although it is recognised that bibliographic tagging and indexing is not always comprehensive, no handsearching of journals will be performed.

Conference proceedings

Given the importance placed on the results of controlled trials, the following conference proceedings will be handsearched for RCTs and CCTs for the last 10 years.

- European Haematology Association
- European Bone Marrow Transplantation Group
- American Society of Haematology
- International Society of Experimental Haematology

The following proceedings were also thought likely to include relevant abstracts; however, these are

indexed on CancerLit so no handsearching will be performed.

- American Society of Clinical Oncology

Classification of studies

Each identified study will be classified by design according to the following list. The classification will determine the nature of data synthesis performed on the study.

1. Prospective randomised controlled trials (RCTs)
2. Well-designed controlled trials with pseudo-randomisation e.g. transplantation given to all patients who have a matched sibling donor (CCTs)
3. Prospective cohort studies with concurrent controls
   Prospective cohort studies with matched data from a national/international registry source
   Prospective cohort studies with historical controls
4. Retrospective cohort studies with concurrent controls
   Retrospective cohort studies with matched data from a national/international registry
   Retrospective cohort studies with historical controls
5. Case series with no matched data (no data from case studies will be included in the systematic review)

Inclusion criteria

1. Studies investigating the efficacy of HDT

All studies will be included if the following criteria are fulfilled:

- the authors state that HDT was administered and the patients received progenitor cell transplants
- the study is investigating, in terms of survival and/or progression-free survival, the effectiveness of HDT
- the study is not a case series.

2. Studies investigating cost-effectiveness

- All articles where the authors state they are investigating the cost-effectiveness of HDT and progenitor cell transplantation.
- All papers where the cost of administering HDT and progenitor cell transplantation in the UK is calculated will be listed, together with the price of treatment.

3. Studies investigating the use of cord-blood transplantation

- All publications where the authors state they have used cord blood as a source of progenitor cells for use in conjunction with HDT.

Assessing eligibility

Titles and abstracts identified by the search strategies (see appendix I) will be assessed for relevance by two reviewers. Copies of all potentially relevant papers will be obtained and rechecked to ensure they fulfil the eligibility criteria. A list of all papers identified by the search strategies, but judged not relevant/ineligible, will be kept.

Data extraction

Two reviewers (one clinical, one non-clinical) will independently classify each study (according to the criteria above) and extract data using the appropriate data extraction sheets (appendix II). Any discrepancies between the classification and data extraction sheets will be discussed and if not agreed upon, the opinion of a third investigator will be sought. All original data extraction sheets will be kept on file.

When it is known that a study has generated multiple publications, the most recent (i.e. that with the most mature data) will be used for data extraction; all previous publications will be catalogued and cross referenced. However, if a second publication reports on a different outcome, e.g. health economics, data will be taken from both papers. It should be noted that it is not always clear when multiple publications relate to the same study, and that this could result in dual reporting of some data. Every effort will be made to ensure that no duplication of RCTs or CCTs occurs.

Methods of analysis

The main conclusions of the systematic review will be based on the results of RCTs/CCTs for all disease sites. If little evidence from RCTs/CCTs is available, then additional information from other cohort studies will be presented; this will be qualitative and no data synthesis will be performed. The decision as to when this additional information is extracted will be made once the number and nature of the eligible studies for each disease site are known, but before any summation of data has been performed. This will take account of the amount of information available and resource implications.

- All eligible RCTs/CCTs will be summarised in tabular format, grouped by disease site and where possible data from these trials will be combined (see statistical analysis section). During preliminary research it has come to our attention that an individual patient data (IPD) meta-analysis of ABMT vs. chemotherapy vs. no further treatment in the treatment of AML has been conducted by the AML Collaborative Group,

the results of which are due to be published in the autumn of 1997.
- Such IPD meta-analyses are the gold standard of systematic reviews and hence any conclusions that arise from the summation of data taken from the literature in this review would be rapidly superseded by those of the AML Collaborative Group. Therefore, although the results of RCT/CCTs in AML will be tabulated, no summation of data will be performed.
- For disease sites where it is judged that little randomised evidence exists, additional tables will be produced summarising the main points of all other eligible studies. No quantitative data synthesis will be performed and information will be presented separately from the RCTs/CCTs.
- For disease sites where it is judged that sufficient evidence from RCTs and CCTs exists, no data extraction from other studies will be performed. However, all other eligible trials will be listed indicating the number of patients treated with HDT.

Tables will also be used to summarise the findings of publications investigating the cost effectiveness of HDT and the use of cord-blood transplantations.

Statistical analysis

For RCTs and CCTs only the data will be combined, if possible, in a series of meta-analyses by disease site on the end-points of survival and disease-free survival.

Where log rank statistics are presented these will be used to calculate hazard ratios for each trial. Otherwise the numbers of events at a series of time-points will be taken from the text or estimated from survival curves. These will be used to calculate the observed and expected number of events and variance at each of those time points and then combined to provide estimates of overall hazard ratios for each trial. In such cases the numbers of events will be adjusted to account for censoring. Pooled hazard ratios will be calculated for each disease site by combining the log rank or estimated O – E and variances for each trial according to the fixed effect model. Results of RCTs and CCTs will be presented separately. Chi-square tests for heterogeneity will be performed and if there is no evidence of gross statistical heterogeneity between the results of RCTs and CCTs, combined results will also be presented.

Results will be presented as a series of standard hazard ratio plots, giving the hazard ratio and confidence intervals (95% and 99%) for each trial as well as the combined hazard ratio and 95% confidence interval.

Appendix I [of protocol]: search strategies

Lymphoma, myeloma, breast, ovarian and testicular cancer

The search strategies are designed to be inclusive to ensure the review is comprehensive. The searches are designed in two sections.

1. A search common to all disease sites which extracts studies concerned with HDT and progenitor cell transplantation
2. A disease specific search

For each disease site, the results of these two searches will be combined to extract studies which appeared in both strategies. This approach will ensure that all papers reporting on the efficacy, cost-effectiveness and long-term side-effects of progenitor cell transplants are identified.

Leukaemia

A preliminary search for leukaemia, using the same general strategy as above, yielded in excess of 10,000 references from Medline alone; a number of references which is not feasible to appraise in the time available. In order to reduce the number of titles identified to a manageable level we have modified the search to be more specific, as outlined below.

A leukaemia specific search was prepared and combined with the bone marrow transplant strategy (as in 1 and 2 above). This was then combined with the search strategy developed by the Cochrane Collaboration to identify controlled trials. A review of the titles discarded by this approach highlighted the fact that potentially relevant publications (other than those reporting on RCTs and CCTs) may be discarded.

In an attempt to ensure that all relevant articles are extracted, the following strategies will be run on the articles previously removed.

For papers with abstracts

- For all papers, those classified by the MeSH heading as 'case studies' were removed.
- Letters, comments and editorials and reviews were removed.
- Papers were removed that did not have one of the following:
  – cost and cost analysis as a MeSH heading
  – financ$
  – econom$
  – surviv$
  – cost$

– event in the same sentence as free
– disease in the same sentence as free
– progression in the same sentence as free
– leukaemia in the same sentence as free.

This strategy is designed to reselect papers reporting on disease/progression and leukaemia free survival, the cost-effectiveness of HDT and long-term toxic effects.

It is possible that by including the above restrictions on the leukaemia subset some studies may have been discarded. Papers excluded during the more specific leukaemia search will be documented.

Details of search strategies

Listed below are the search strategies designed for use on Medline. The searches will be modified for use with other databases.

Key to search strategies

.de. the term used is a MeSH heading
# MeSH heading was exploded (i.e. all subheadings were included in the search)
$ any character or string of characters
adj words adjacent
with words appear in same sentence
pt publication type

Progenitor cell transplantation search

1. hematopoietic-stem-cells#.de.
2. bone-marrow-transplantation#.de.
3. hematopoietic-stem-cell-transplantation#.de.
4. transplantation-homologous.de.
5. transplantation-autologous#.de.
6. salvage-therapy#.de.
7. (marrow with transplant$).ti,ab.
8. (stem$ with transplant$).ti,ab.
9. high adj dose adj therapy.ti,ab.
10. autograft.ti,ab.
11. autologous adj transplant$.ti,ab.
12. allogeneic adj transplant$.ti,ab.
13. allograft.ti,ab.
14. myeloablative.ti,ab.
15. hematopoietic adj stem adj cells
16. bone-marrow-purging#.de.
17. hematopoietic adj stem adj cell
18. cord adj blood.ti,ab.
19. fetal-blood.de.
20. animal
21. human
22. 20 not (21 and 20)
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
24. 23 not 22

Breast

1. breast-neoplasms#.de.
2. cancer
3. neoplasms#.de.
4. carcinoma
5. breast
6. 2 with 5
7. 3 and 5
8. 4 with 5
9. 1 or 6 or 7 or 8
10. surgical-flaps.de.
11. reconstruction.ti,ab.
12. 10 or 11
13. 9 not 12

The above search will identify papers which have one of the following:
Breast neoplasm (MeSH term)
'breast' and 'cancer' in the same sentence
'breast' and 'carcinoma" in the same sentence
Neoplasm as a MeSH heading with 'breast' in the reference.

It will remove papers which have one of the following:
'reconstruction' in the title
'Surgical flaps' as a MeSH heading.

Ovarian

1. Ovarian-Neoplasms#.
2. ovar$
3. Neoplasms#.de.
4. cancer
5. carcinoma
6. 2 and 3
7. 2 with 4
8. 2 with 5
9. 1 or 6 or 7 or 8

The above search will identify papers which have one of the following:
Ovarian neoplasm as a MeSH heading
Neoplasm as a MeSH heading with ovar$ in the reference
'cancer' and 'ovar$' in the same sentence
'Carcinoma' and 'ovar$' in the same sentence.

Testicular

1. testicular-neoplasms#.de.
2. neoplasms#.de.
3. cancer
4. testi$
5. germ adj cell
6. nsgct
7. teratoma
8. germinal
9. seminoma

10. testes
11. germinoma
12. 2 and 4
13. 2 and 5
14. 2 and 8
15. 2 and 10
16. 3 with 4
17. 3 with 5
18. 3 with 8
19. 3 with 10
20. carcinoma
21. 20 with 4
22. 20 with 5
23. 20 with 8
24. 20 with 10
25. 1 or 6 or 9 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 21 or 22 or 23 or 24

The above search will identify papers which have one of the following:
testicular neoplasm as a MeSH heading
'teratoma' in the reference
'seminoma' in the reference
'germinoma' in the reference
NSGCT in the reference
Neoplasm as a MeSH heading with testi$ or germ cell or testes or germinal in the reference
'carcinoma' and 'testi$' in the same sentence
'carcinoma' and 'germ cell' in the same sentence
'carcinoma' and 'testes' in the same sentence
'carcinoma' and 'germinal' in the same sentence
'cancer' and 'testi$' in the same sentence
'cancer' and 'germ cell' in the same sentence
'cancer' and 'testes' in the same sentence
'cancer' and 'germinal' in the same sentence.

Lymphoma

1. Lymphoma#.de.
2. burkitt$
3. lymphoma
4. hodgkin$
5. NHL
6. HD
7. 1 or 2 or 3 or 4 or 5 or 6

Myeloma

1. myeloma
2. Multiple-Myeloma.de.
3. myelomatosis
4. 1 or 2 or 3

Leukaemia

1. hematopoietic-stem-cells#.de.
2. bone-marrow-transplantation#.de.
3. hematopoietic-stem-cell-transplantation#.de.
4. transplantation-homologous#.de.
5. transplantation-autologous#.de.
6. salvage-therapy#.de.
7. (marrow with transplant$).ti,ab.
8. (stem$ with transplant$).ti,ab.
9. high adj dose adj therapy.ti,ab.
10. autograft.ti,ab.
11. autologous adj transplant$.ti,ab.
12. allogeneic adj transplant$.ti,ab.
13. allograft.ti,ab.
14. myeloablative.ti,ab.
15. hematopoietic adj stem adj cells
16. bone-marrow-purging#.de.
17. hematopoietic adj stem adj cell
18. animal.de.
19. human.de.
20. 18 not (18 and 19)
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
22. 21 not 20
23. leukemia#.de.
24. leukemia
25. aml
26. all
27. cml
28. cgl
29. cll
30. feline or cat
31. bovine
32. mouse
33. 30 or 31 or 32
34. 23 or 24 or 25 or 26 or 27 or 28 or 29
35. 34 not 33
36. pt=randomized-controlled-trial
37. randomized adj controlled adj trials.de.
38. random adj allocation.de.
39. double adj blind adj method.de.
40. single adj blind adj method.de.
41. 36 or 37 or 38 or 39 or 40
42. pt=clinical-trial
43. clinical-trials#.de.
44. (clin$ with trial$).ab,ti.
45. ((singl$ or doub$ or treb$ or trip$) adj (blind$ or mask$)).ab,ti.
46. placebos.de.
47. placebo$.ab,ti.
48. random.ab,ti.
49. research adj design.de.
50. 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. comparative adj study.de.
52. evaluation-studies#.de.
53. follow-up-studies.de.
54. prospective-studies.de.
55. (control$ or prospectiv$ or volunteer$).ti,ab.
56. 50 or 51 or 52 or 53 or 54 or 55
57. 41 or 50 or 56
58. 22 and 35
59. 57 and 58
60. 58 not 59

61. 60 ab = y
62. (event with free).ti,ab.
63. (disease with free).ti,ab.
64. (progress$ with free).ti,ab.
65. (leukemia with free).ti,ab.
66. financ$.ti,ab.
67. surviv$.ti,ab.
68. cost$.ti,ab.
69. survival-analysis#.de.
70. costs-and-cost-analysis#.de.
71. econom$.ti,ab.
72. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71
73. 61 and 72
74. 60 not 61
75. 73 or 74
76. 59 or 75
77. case-report.de.
78. pt=comment or pt=editorial or pt=guideline or pt=letter
79. 77 or 78
80. 76 not 79
81. review.pt.
82. 80 not 81

Appendix II [of protocol]: data extraction sheets

The data extraction sheets for clinical studies relating to survival have been designed in several parts.

Part 1 Introductory sheets common to all papers including information such as the title, authors, topic of the paper/abstract and specific information about the study.

Part 2a **For papers investigating the efficacy of HDT**
Sheets for specific information about the study, patient characteristic and study results.

Part 2b **For papers investigating the cost-effectiveness of HDT**
Sheets for specific information about the methods and results of the study.

Part 3 A conclusion/discussion sheet common to all papers.

Key to data extraction study classification codes

RCT	Prospective randomised clinical trials
CCT	Well-designed controlled trials with pseudo-randomisation e.g. transplantation will be given to all patients who have a matched sibling donor
PHII	Well-designed prospective Phase II trial, no randomisation
PC	Prospective cohort studies with concurrent controls from same centre
PR	Prospective cohort studies with matched data from a national/international registry source
PH	Prospective cohort studies with historical controls from same centre
RC	Retrospective cohort studies with concurrent controls from same centre
RR	Retrospective cohort studies with matched data from a registry
RH	Retrospective cohort studies with 'historical controls'

Definitions of status at high-dose therapy

First-line treatment	HDT given as the initial therapy, no prior chemotherapy is given.
First remission	Patient received HDT after conventional dose remission induction therapy and achieves either a complete or partial remission.
Sensitive relapse	Objective response to second line conventional dose therapy, including second CR or PR.
Resistant relapse	Patient receives an initial response and then subsequently relapses. Further conventional dose salvage therapy is given but the patient has no response.
Untreated relapse	Patient proceeds immediately to HDT with no conventional dose salvage therapy to test responsiveness.
Primary refractive	Patient fails to achieve an objective response to their initial or disease second or third line conventional dose chemotherapy.

Data extraction sheet - Efficacy papers

Reference number Database number Trial Group Trial Code

Details of publication

Title:

Authors:

Source:

Country:

English ☐ Other Language (specify): _____

Summary of question being addressed:

Economic evaluation Yes ☐ No ☐ Q of L assessment Yes ☐ No ☐

Study design

RCT ☐
CCT ☐
PHII ☐
PC ☐
PR ☐
PH ☐
RC ☐
RR ☐
RH ☐

Single centre ☐ Multi centre ☐

Patient entry dates:

RCT/CCT - Method of randomisation:

Phone ☐ Envelope ☐
DOB ☐ Availability of a sibling ☐
Other - specify _____

For non-randomised studies - was patient entry:

Sequential ☐
Determined by guidelines ☐
No mention ☐

Point of randomisation:

Eligibility criteria

Leukemia
Acute myeloid ☐
Acute lymphoblastic ☐
Chronic myeloid ☐
Chronic lymphocytic ☐

Lymphoma
HD ☐
NHL ☐

Testicular
Seminoma ☐
Non seminoma ☐

Ovarian ☐
Breast ☐
Myeloma ☐

Any further sub - class ?

Major eligibility criteria -

High Dose Therapy

Allogeneic ☐ Autologous ☐ Both ☐

Bone marrow ☐ Stem cells ☐ Both ☐

Cord blood ☐

Transplant purged Yes ☐ No ☐ Both ☐

Details of HDT (tick all that apply)	Yes	If mixed Num	%
Chemotherapy only	☐	☐	☐
Chemotherapy and TBI	☐	☐	☐
Chemotherapy and targeted radiotherapy	☐	☐	☐

Baseline characteristics

	HDT	Conv chemo	3rd arm
No of patients			
% eligible			
% starting therapy			

	HDT	Conv chemo	3rd arm
Male:female			
Median age			
Age range			

Were the arms of the trial study balanced in terms of prognostic factors? Yes ☐ No ☐ ? ☐

Was the trial stratified? Yes ☐ No ☐ ? ☐

If yes, by what: _____

Status at High Dose Therapy If mixed

(Tick all that apply)

	Yes	Num	%
First line treatment	☐	☐	☐
First remission (CR or PR)	☐	☐	☐
Sensitive relapse	☐	☐	☐
Resistant relapse	☐	☐	☐
Untreated relapse	☐	☐	☐
Primary refractory disease	☐	☐	☐
Adjuvant	☐	☐	☐

Other (specify)

Results

Intention to treat analysis Yes ☐ No ☐ ? ☐

Median follow up (months) ☐ Min ☐ Max ☐

Survival

Hazard Ratio		95% / 99% CI	
Odds Ratio		95% / 99% CI	
O-E			
V			
χ^2 Value			
p - value			

	HDT	Conv chemo	3rd arm
% survival at 6 months			
% survival at 1 year			
% survival at 2 years			
% survival at 5 years			

Median survival (CI) ☐

Was a subgroup analysis performed? Yes ☐ No ☐

Results of subgroup analysis:

Other significant results:

Progression free survival

Hazard Ratio		95% / 99% CI	
Odds Ratio		95% / 99% CI	
O-E			
V			
χ^2 Value			
p - value			

	HDT	Conv chemo	3rd arm
% survival at 6 months			
% survival at 1 year			
% survival at 2 years			
% survival at 5 years			

Median progression-free survival (CI)

Was a subgroup analysis performed? Yes ☐ No ☐

Results of subgroup analysis:

Other significant results:

Toxicity

Treatment related

	HDT	Conv chemo	3rd arm
No of early deaths ≤90 days			
No of late deaths ≥90 days			
Time not specified			

Details of haemapoetic recovery given Yes ☐ No ☐ ? ☐

Reviewer's comments/criticism

General

Comments on further trials to be done/ongoing.

Cost effectiveness

Reference number | Database number | Trial Group | Trial Code

Details of publication

Title:

Authors:

Source:

Country:

English ☐ Other Language (specify): _____

Summary of question being addressed:

Study type: CBA ☐ CUA ☐ CEA ☐ Calculation of UK costs ☐ Other _____

Costs taken into account

Direct costs		**Yes**	**No**	**List any indirect costs**
Programme costs	Diagnosis and Therapy	☐	☐	
	Professional fees	☐	☐	
	Drugs	☐	☐	
	Ward	☐	☐	
	Nursing	☐	☐	
Additional provider costs	Insurance	☐	☐	
	Set up costs	☐	☐	
Patient costs		☐	☐	
Family costs		☐	☐	
Do estimated costs include				
Getting patient into remission (if applic)		☐	☐	
Treating subsequent remissions		☐	☐	
Treating secondary malignancies (if applic)		☐	☐	

Source of data

Clinical information

Was data taken from a randomised comparison? Yes ☐ No ☐ ? ☐

Collected: Prospectively ☐ Retrospectively ☐

Source: Single trial/study ☐ Multiple trials/studies ☐ Syst rev of trials/studies ☐ Rev of pat notes ☐

If trial/study was data taken from:

Published papers ☐

Unpublished work ☐

Unpublished/published ☐

If info from patient notes was data extracted by:

Single person looked at all notes ☐

Several people looked at notes ☐

Two people looked at each set of notes ☐

Years clinical info taken from: _____

Estimation of total quantities of resources used

Based on actual data ☐ Estimated ☐ Based on model ☐ State model: _____

Estimation of total costs

Based on actual data ☐ Estimated ☐ Based on model ☐ State model: _____

Years cost data taken from: _____ Year of final cost assessment: _____

Were costs inflated? Yes ☐ No ☐ ? ☐ Currency unit reported: _____

Was a conversion done from original currency? Yes ☐ No ☐ Original currency: _____

Quality of life assessment

Prospectively ☐ Retrospectively ☐ None ☐

Assignment of values to health states (if appl) Drs ☐ Nurses ☐ Patients ☐ Healthy Volunteers ☐

Results

Length of time horizon ☐

	BMT	Conventional treatment	Difference *
Cost of treatment ± SD			
Life years saved ± SD			
QALY saved ± SD			

*If BMT more expensive +ve, if -ve less expensive

Cost per life year gained by transplantation ☐ Were sensitivity analyses carried out

Yes ☐ No ☐

Cost per QALY gained by transplantation ☐ Details:

Were any costs discounted? Yes ☐ No ☐ Details:

If analysis repeated with a "normal life expectancy tail"

Length of survival tail

	BMT	Conventional treatment	Difference *
Cost of treatment ± SD			
Life years saved ± SD			
QALY saved ± SD			

*If BMT more expensive +ve, if -ve less expensive

Cost per life year gained by transplantation

Were sensitivity analyses carried out

Yes ☐ No ☐

Cost per QALY gained by transplantation

Details

Were any costs discounted? Yes ☐ No ☐

Details:

Reviewers comments/criticism

Long-term Toxicity

Reference number | Database number | Trial Group | Trial Code

Details of publication

Title:

Authors:

Source:

Country:

English ☐ Other Language (specify): _____

Summary of question being addressed:

Investigating incidences of (tick all that apply):

- Second malignancies ☐
- Cardiac abnormalities ☐
- Respiratory abnormalities ☐
- Gonadal function ☐
- Cataracts ☐
- Other ☐
- Myelodysplasia ☐

Specify _____

Diseases included in test cohort

- Leukaemia ☐
- Lymphoma ☐
- Myeloma ☐
- Breast ☐
- Other ☐

Specify _____

High Dose Therapy

Details of transplant

	No receiving		No receiving
Allogeneic		Autologous	
Bone marrow		Stem cells	
Purged		Unpurged	

Details of high dose therapy

	No receiving
Chemotherapy only	
Chemotherapy and TBI	
Chemotherapy and targeted radiotherapy	
Cyclophosphamide containing regimens	

Details of patient cohorts

	Test cohort	Control cohort
Source of		
Patient entry dates		
Median time from BMT (months)		
Min time (months)		
Max time (months)		

Was comparison randomised: Yes ☐ No ☐ ? ☐

Details of patient cohorts cont.

	Test cohort	Control cohort
No of patients		
Male:female		
Age range at BMT		
Median age at BMT		

Were control cohort matched for age and prognostic factors? Yes ☐ No ☐ ? ☐

Clinical information collected: Prospectively ☐ Retrospectively ☐

Results

Summarise the major results, including statistics and incidence of long-term toxicities

Reviewers comments

Appendix 2

Relevant RCTs that did not report on one of the two specified end-points of survival or PFS

Cassano W. A comparison of allogeneic bone marrow transplantation, autologous transplantation, or maintenance chemotherapy for the treatment of childhood acute lymphocytic leukemia in second remission. *Proc Annu Meet Am Soc Clin Oncol* 1993;**12**:A1058.

Rohatiner AZS, Johnson PWM, Price CGA, Arnott SJ, Amess JAL, Norton AJ, *et al.* Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for recurrent follicular lymphoma. *J Clin Oncol* 1994;**12**(6):1177–84.

Appendix 3

Glossary

Allogeneic transplantation	Transplant which uses haemopoietic progenitor cells harvested from a donor, either a sibling or unrelated donor.
Autologous transplantation	Transplant which uses the patient's own haemopoietic progenitor cells, harvested prior to the high-dose chemotherapy or radiotherapy.
Bone marrow transplantation	Transplant in which progenitor cells are collected from the bone marrow.
Complete remission	Response where disease is no longer detectable, usually by clinical criteria.
Consolidation therapy	Therapy given to a patient once they have reached a complete or partial remission. The aim of treatment is to increase the duration of remission.
Controlled clinical trial	Used in this report to mean a prospectively conducted trial in which the allocation of treatment is pseudo random, for example by donor availability.
Cord blood	Placental blood harvested from the umbilical cord just after birth. Progenitor cells from the umbilical cord can be used for transplantation, and have the advantage that their immune function is not fully developed, which may reduce the risk of graft versus host disease associated with allogeneic and unrelated donor transplantation.
First-line therapy	Initial treatment given to a patient after which it is intended that no further therapy is given (unless the disease relapses).
Graft versus host disease	Immune reaction of the donor marrow to the transplant recipient. Usually manifests in skin rashes, gut toxicity and liver damage; a detrimental effect.
Graft versus leukaemia	Immune reaction of the donor marrow to the residual leukaemia cells of the recipient; a beneficial effect.
Haemato-poietic recovery	Increase in the levels of blood cells to normal levels following myeloablative chemotherapy.
Hazard ratio	Overall chance of failure on treatment compared to control. Measure of the relative survival experience of two patient groups which accounts for individual survival times and allows for censoring of patients.
High-dose therapy	Used in this report to mean myeloablative therapy including PCT transplantation.
Induction	Initial treatment given to a patient. In most cases, patients responding to induction treatment will receive further consolidation therapy.
Log rank test	Statistical method used to compare actuarial survival curves.
Matched sibling donor	A sibling whose tissue type immunologically matches the patient's and can be donated for transplantation. The likelihood of a sibling being a match is 1 in 4.
Matched unrelated donor	An unrelated donor whose tissue type is significantly well immunologically matched to a patient's so that their stem cells can be used for transplantation.
Myeloablative therapy	Chemo- or chemoradiotherapy which has as one of its side-effects the permanent or near-permanent destruction of bone-marrow function.
Odds ratio	Chance of failure on treatment compared with control at a particular point in time. Calculation uses only number of events and takes no account of the censoring of patients.
Partial remission	Response of a disease to therapy which is not complete but is considered to indicate that the tumour is sensitive to the therapy administered. For example, a decrease of at least 50% in the product of two diameters of all tumours compared with that before treatment.
Peripheral blood stem cell	Stem cells that are harvested from the peripheral blood circulation rather than from the bone marrow. Stem cells are naturally found in the bone marrow, but the administration of chemotherapy with or without granulocyte colony stimulating factors causes over-

	production of the cells resulting in significant concentrations in the general circulation.
Peripheral blood stem cell transplantation	Progenitor cell transplantation using stem cells harvested from the systemic circulation.
Progenitor cell	Precursor blood cell found in most abundance in the bone marrow, from which all blood cells develop. Also called a stem cell.
Progenitor cell transplantation	Term used to describe the harvesting of progenitor cells and the subsequent administration of these cells to a patient following myeloablative therapy.
Progression-free survival	The length of time that a patient remains alive, without any progression of disease.
Randomised controlled trial	Prospectively conducted trial in which participants are randomly assigned to receive or not receive a particular intervention. The aim of randomisation is to ensure that treatment groups are balanced for both known and unknown prognostic factors and that any observed differences in outcome are due to the intervention and not to differences in patient population.
Stem cell	Alternative name for a progenitor cell.

Appendix 4

Physicians data query

Physicians data query (PDQ) is a comprehensive cancer database set up by the US National Cancer Institute available on the Internet. It contains peer-reviewed statements on treatment, supportive care, prevention, and screening, as well as anti-cancer drugs; a registry of over 1600 open and 8000 closed clinical trials from around the world; and directories of physicians and organisations that provide cancer care in the USA.

The registry of trials provides detailed information on a large number of open and closed studies (Phase I–IV) from the USA and around the world. Like any trials database PDQ is not comprehensive; not only does it rely on protocols being submitted to the registry, but also, like all information on PDQ, protocols are indexed subject to peer review.

Access

The web site address for PDQ is www/icic.nci.nih.gov/pdq/pdq_dm.htm and much of the information contained in the database is available to all with Internet access. However to search and browse the trials registry it is necessary to become a member of the NCI Information Associates Program. Further information can be obtained on www/icic.nci.nih.gov/jnci/iapinfo.html.

Trial coding

Protocols are indexed on PDQ with a unique trial code and for on-going and as yet unpublished trials identified through PDQ it is this code that appears in the lists of on-going trials in each chapter of this review.

Appendix 5

Summary of the EBMT classification for HDT and the findings of this review

The EBMT HDT classification below is taken from a special report published by the EBMT in 1996[1] which aimed to 'define what might be regarded as current or standard transplant practice in Europe' at the time of publication. The authors stress that the information contained in the paper should not be used to discourage or prevent innovative procedures in this field and that the indications for the use of HDT are ever changing. *Tables 74* and *75* also summarise the results of the present review. It must be reiterated that for the majority of disease sites investigated there were very few randomised or psuedo-randomised trials and therefore the data summarised here should be regarded as preliminary.

TABLE 74 *Comparison of the EBMT HDT guidelines and the findings of the present systematic review for autologous transplantation*

Disease	EBMT guidelines*	Findings of the systematic review†
AML: adult first CR	Routine	No evidence of an OS difference, possible PFS advantage in favour of HDT.
AML: paediatric first CR	Routine	Possibility of an OS advantage in favour of CC. No evidence of a difference in PFS.
AML: second or third CR, incipient relapse	Routine	No reliable information.
AML: relapse	Not recommended	No reliable information.
ALL: paediatric, low risk, second CR	Routine	No reliable information.
ALL: paediatric, high risk, first CR	Routine	No reliable information.
ALL: adult, high risk, first CR/second CR, incipient relapse	Routine	No evidence of a difference between treatments.
ALL: adult, established relapse	Not recommended	No reliable information.
CML: chronic phase	Protocol	No reliable information.
CML: advanced phase	Protocol	No reliable information.
CML: blast crisis	Not recommended	No reliable information.
NHL: intermediate/high grade, first CR	Routine	No evidence of an OS or PFS difference.
NHL: low-grade relapse or second CR	Protocol	No reliable information.
NHL: intermediate/high grade, second or third CR	No comment made	Insufficient evidence to draw conclusions; single trial reported an OS and PFS benefit in favour of HDT.
HD: first CR	Protocol	No reliable information.
HD: first relapse, or second or third CR	Routine	Insufficient evidence to draw conclusions. (Single small trial reported PFS advantage in favour of HDT but found no evidence of an OS benefit in relapsed/refractory patients.)

* *Routine = HDT in routine use for selected patients; Protocol = HDT to be undertaken in approved Clinical Research Protocols; Pilot = HDT used in developmental or pilot studies can be approved in specialist units.*

† *No reliable information = no RCT/CCTs identified; OS = overall survival.*

continued

TABLE 74 contd *Comparison of the EBMT HDT guidelines and the findings of the present systematic review for autologous transplantation*

Disease	EBMT guidelines*	Findings of the systematic review†
HD: refractory	Pilot	Insufficient evidence to draw conclusions. (Single small trial reported PFS advantage in favour of HDT but found no evidence of an OS benefit in relapsed/refractory patients.)
Myeloma: stage I	Protocol	No reliable information.
Myeloma: other stages	Routine	No evidence of a difference in OS. Possible PFS benefit in favour of HDT.
Breast cancer: adjuvant	Protocol	No reliable information.
Metastatic breast cancer responding	Protocol	Insufficient information reported in trials to allow quantitative data summation or conclusions to be drawn.
Germ-cell tumours	Protocol	Insufficient evidence to draw conclusions. (Single small trial reported PFS advantage in favour of HDT but found no evidence of an OS benefit.)
Ovarian cancer: minimal disease	Pilot	No reliable information.
Small cell lung cancer: limited disease	Pilot	Insufficient evidence to draw conclusions. (Single small trial found no evidence of an OS difference, but gives possibility of PFS advantage in favour of HDT.)

* *Routine = HDT in routine use for selected patients; Protocol = HDT to be undertaken in approved Clinical Research Protocols; Pilot = HDT used in developmental or pilot studies can be approved in specialist units.*

† *No reliable information = no RCT/CCTs identified; OS = overall survival.*

TABLE 75 *Comparison of the EBMT HDT guidelines and the findings of the present systematic review for allogeneic transplantation*

Disease	EBMT guidelines*	Findings of the systematic review†
AML: adult first CR	Routine	No evidence of an OS difference. Possibility of a PFS advantage in favour of HDT.
AML: paediatric first CR	Routine	Possibility of an OS and PFS advantage in favour of HDT.
AML: second or third CR, incipient relapse	Routine	No reliable information.
AML: relapse	Pilot	No reliable information.
ALL: paediatric, low risk, second CR	Routine	Trial gives insufficient information to draw any conclusions (trial included all risk category patients).
ALL: paediatric, high risk, first CR	Pilot studies	Insufficient evidence to draw conclusions. (Single trial found no evidence of a difference in OS or PFS.)
ALL: adult, high risk, first CR/second CR, incipient relapse	Routine	No evidence of an OS difference between treatments. Possible PFS benefit in favour of HDT.
ALL: adult, established relapse	Pilot	No reliable information.
CML: chronic phase	Routine	No reliable information.
CML: advanced phase	Routine	No reliable information.
CML: blast crisis	Pilot	No reliable information.
NHL: intermediate/high grade, first CR	Routine	No reliable information.
NHL: low-grade relapse or second CR	Protocol	No reliable information.
NHL: intermediate/high grade, second or third CR	No comment was made	No reliable information.
HD: first CR	Not recommended	No reliable information.
HD: first relapse, or second or third CR	Protocol	No reliable information.
HD: refractory	Not recommended	No reliable information.
Myeloma: stage I	Protocol	No reliable information.
Myeloma: other stages	Routine	No reliable information.

* *Routine = HDT in routine use for selected patients; Protocol = HDT to be undertaken in approved Clinical Research Protocols; Pilot = HDT used in developmental or pilot studies can be approved in specialist units.*

† *No reliable information = no RCT/CCTs identified; OS = overall survival.*

Appendix 6

Introduction to individual patient data meta-analysis

The systematic review reported here aimed to review the published data comparing the efficacy of HDT/PCT with that of CC. During the research and preparation of the review it became evident, as with many systematic reviews of the literature, that much of the required information was not presented in the published trial reports and this prevented complete analyses of the data. In addition it became apparent that there were several trials that were completed but were as yet unreported and so could not be included in this review. These problems are just two of the many drawbacks of conducting systematic reviews or meta-analyses of the literature.

The gold standard for meta-analysis is widely believed to be one based on individual patient data (IPD). In such an analysis, updated data for all patients entered into all trials known to have been conducted worldwide, both published and unpublished, are obtained. The study mentioned in chapters 6 and 7 conducted by the AML Collaborative Group is an example of an IPD meta-analysis and as this followed stricter, more robust methodology, its findings are likely to be more reliable than those reported in this review.

Summary of the shortcomings of meta-analyses of the published literature (MAL) compared with meta-analyses of individual patient data (MAP) (adapted from Stewart and Parmar, 1993[9])

A MAL depends only on the information presented in published reports, and the specific data required for analysis may not be available. Abstracts, especially, seldom contain detailed information and full papers may concentrate on end-points other than the one of primary interest. Journals and, more commonly, investigators themselves are more likely to publish positive results, and publication bias alone can influence meta-analysis. A MAP does not rely on published information alone but includes all available trial data, both published and unpublished. The trial protocol and 'raw' data are obtained and checked by the meta-analyst.

Meta-analyses are often restricted to the analysis of reliable evidence from randomised trials. However, not all studies reported to be randomised can be assumed to be free of bias. On detailed inspection it may emerge that the clinician could have known in advance which treatment a patient would be allocated (for example, if the patient's date of birth had been used as the means of 'randomisation') and on the basis of this prior knowledge decide whether or not to enter the patient into the trial. Some methods of randomisation, such as sealed envelopes, may also be insecure. This is particularly pertinent to the trials reported here which compared allogeneic transplantation with conventional therapy because it is difficult to ascertain from a published report whether all patients included in the analysis underwent, along with potential sibling marrow donors, HLA typing. A MAP can assess the method of randomisation (or in the case of allogeneic transplant trials, the validity of HLA typing procedures) from the trial protocol and further examine the integrity of randomisation using individual patient data and on the basis of this identify trials that have been properly randomised. Such checks cannot be made in a MAL.

Patients in a randomised trial should be analysed by allocated treatment whether or not they received that treatment. Not all trials do this. A MAP permits analysis by intention to treat even if the published report did not do so. Clearly, a MAL is restricted to using information from the published analysis even if this analysis is flawed. It is often not clear from publications how many patients have been excluded from the original analyses. Exclusions can be especially problematic with older trials.

Pressure to publish quickly often results in short follow-up so MALs tend to focus on early time-points which may be inappropriate in a chronic disease.

A MAP permits a more sensitive analysis. As is the case here, a MAL commonly uses either the total reported number or proportion of deaths on each arm at a particular time. This gives an OR at this specified time-point. The number of deaths

often has to be estimated from survival curves and although the number of patients at risk should be adjusted to take account of censoring, this is not always possible. Unless the death rate on each treatment arm is constant throughout the trial (the hazards are proportional), the OR should be applied only to the time-point for which it was generated. It therefore reflects little of the rest of the survival experience and might misrepresent the underlying treatment effect, especially if based at points of maximum or minimum difference.

By contrast a MAP commonly uses survival times of individual patients to calculate HRs which average the treatment effect over time, giving an estimate of the overall relative benefit of treatment. For a particular time-point the absolute benefit can be estimated from the HR and the survival rate in the control group. Where the main end-point is binary (e.g. it is survival itself rather than length of survival that is important) or where the event rate is low, it may be acceptable to use the numbers dead and alive at a time-point beyond the period during which most disease-related deaths take place. However, in most chronic diseases length of survival is of major importance. For many types of cancer the survival curves for two competing treatments may separate initially but are likely to converge at some point during the period of interest. In such instances early in time an OR will tend to over-estimate the underlying treatment effect and late in time it will tend to underestimate it. The HR and survival curve from a MAP is more informative and more helpful clinically.

MAPs can also address important supplementary questions, and in particular, whether treatment is more or less effective in well-defined groups of patients. As a result of the variations between trials in the number of patients included and the implicit heterogeneity between trials, a MAP currently provides the best means of addressing such issues.

HTA panel membership

This report was identified as a priority by the Acute Sector Panel.

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