Clinical effectiveness and cost-effectiveness of stem cell transplantation in the management of acute leukaemia: a systematic review

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Executive summary

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Executive summary

Background

Acute leukaemia is a group of rapidly progressing cancers of bone marrow and blood. It is broadly classified as either acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL). Acute leukaemia can occur at any age. The incidence of AML rises sharply in middle age and is highest among older people, whereas ALL occurs mainly in children and younger adults.

Conventional chemotherapy has varied degrees of success in treating acute leukaemia, and long-term survival for many patient groups remains poor. Different forms of haemopoietic stem cell transplantation (SCT) have been used in addition to or in place of chemotherapy at various stages of the treatment pathway in the hope of improving survival and/or quality of life. Much research has been done on the effectiveness of SCT (and, to a lesser extent, its cost-effectiveness), including systematic reviews and meta-analyses. These have used different methodologies, dealt with different types of SCT and/or different types of leukaemia and/or different age groups, and many may not be sufficiently up to date. Consequently, it is difficult to easily identify which aspects of the effectiveness of SCT are supported by both a good quality and a good quantity of evidence and which areas require priority for further research.

Objectives

This report aims to provide a systematic overview of the best available evidence on the clinical effectiveness and cost-effectiveness of SCT in the treatment of acute leukaemia. The specific objectives were: (1) to systematically identify and review published systematic reviews, meta-analyses and economic literature in this field; (2) to systematically identify new evidence from randomised controlled trials (RCTs) and donor versus no donor (DvND) studies that has not been included in previous reviews and meta-analyses; and (3) to map information from the above two sources and generate an inventory of best available evidence to help inform the commissioning of future research.

Methods

A systematic review of published systematic reviews and meta-analyses was carried out. Electronic databases including MEDLINE, EMBASE and the Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and NIHR Health Technology Assessment (HTA) databases] were searched from inception to December 2008. Retrieved records were screened for relevance. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and meta-analyses were critically appraised and data were extracted and narratively presented.

A separate search of RCTs and DvND studies was performed. Cochrane CENTRAL (Central Register of Controlled Trials), MEDLINE, EMBASE and SCI (Science Citation Index) were searched from 1997 to March 2009. Retrieved records were screened and relevant papers were selected following the same procedure described above. Included RCTs and DvND studies were mapped to the evidence covered in existing systematic reviews and meta-analyses according to a framework of 12 decision problems (DPs): DP1 related to SCT in adults with AML in first complete remission (CR1); DP2 related to adults with AML in second or subsequent remission or with refractory disease (CR2+); DP3 related to children with AML in CR1; DP4 related to children with AML in CR2+; DP5 related to adults with ALL in CR1; DP6 related to adults with ALL in CR2+; DP7 related to children with ALL in CR1; DP8 related to children with ALL in CR2+; DP9 related to comparison of different sources of stem cells in transplantation in any acute leukaemia or age group; DP10 related to different conditioning regimens; DP11 related to the use of purging in autologous stem cell transplantation (autologous SCT); and DP12 related to the use of T-cell depletion in allogeneic stem cell transplantation (allogeneic SCT). Evidence from new RCTs and DvND studies not covered in existing reviews and meta-analyses was briefly described alongside evidence from existing reviews in each decision problem. In addition, research registers were searched for ongoing trials

and relevant studies were mapped to individual decision problems.

For the cost-effectiveness review, MEDLINE, EMBASE, DARE and NHS Economic Evaluation Database (EED) (via the Cochrane Library) were searched from inception to January 2009. Retrieved records were screened and relevant economic literature, including full economic evaluations and cost studies, was selected and reviewed by one reviewer. Results were tabulated and described narratively.

Results

Volume and quality of available systematic reviews and meta-analyses

Fifteen systematic reviews and/or meta-analyses published between 1998 and 2008 met the inclusion criteria. These included five systematic reviews (without quantitative synthesis of evidence), six meta-analyses (with or without systematic searches of literature), three individual patient data meta-analyses and one HTA report. Thirteen of the included reviews/meta-analyses were published from 2004 onwards. Nine studies searched MEDLINE only and three did not describe any search of literature. Ten reviews/meta-analyses focused on evidence from RCTs and/or DvND studies, whereas the other five included broader evidence from cohort studies and/or case series. DP1 (adults with AML in CR1) was covered in seven reviews/meta-analyses, whereas relatively few reviews/meta-analyses covered children and adult patients in second complete remission and beyond (CR2+). Taking into account the timing of their publications, most reviews appeared to have omitted an appreciable proportion of potentially available evidence when the lists of included studies in existing reviews addressing the same decision problem were cross-checked against each other.

Clinical effectiveness of allogeneic SCT

The best available evidence concerning the effectiveness of allogeneic SCT using stem cells from matched sibling donors came from DvND studies. Among DPs 1–8, there was sufficient evidence from DvND studies to support the use of allogeneic SCT in DP1 (adult AML in CR1 – except in good-risk patients), DP3 (childhood AML in CR1 – role of risk stratification unclear) and DP5 (adult ALL in CR1 – role of risk stratification unclear). There was some conflicting evidence in DP7 (high-risk childhood ALL in CR1) and a paucity of evidence from DvND studies for all the decision problems concerning various patient groups in CR2+. Evidence concerning allogeneic SCT using stem cells from matched unrelated donors was lacking.

Clinical effectiveness of autologous SCT

The best available evidence came from RCTs. Sufficient evidence from RCTs was available for DP1 (adult AML in CR1), DP3 (childhood AML in CR1) and DP5 (adult ALL in CR1). Overall, the evidence suggested that autologous SCT was either of similar effectiveness to or less effective than chemotherapy. Evidence from RCTs for the other decision problems was either lacking or very limited and did not favour autologous SCT over chemotherapy.

Other comparisons

There was a paucity of evidence from RCTs comparing different sources of stem cells (DP9), different conditioning regimens (DP10), purging versus no purging (DP11), and T-cell depletion versus no depletion (DP12) in existing reviews. However, there was emerging evidence from RCTs for DP9 and DP10.

Areas warranting further synthesis of evidence

Our searches of RCTs and DvND studies found a sufficient volume of new evidence to warrant conducting new reviews in DP4 (childhood AML in CR2+, new DvND studies), DP5 (adult ALL in CR1, new DvND studies and RCTs), DP7 (childhood ALL in CR1, new DvND studies), DP8 (childhood ALL in CR2, new DvND studies), DP9 [new RCTs comparing bone marrow transplantation (BMT) with peripheral blood stem cell transplantation (PBSCT)] and DP10 [ongoing RCTs comparing reduced intensity conditioning (RIC) with myeloablative conditioning regimens]. Other decision problems were either covered in sufficiently up-to-date systematic reviews or lacking sufficient new evidence.

Review of cost-effectiveness

Nineteen studies met the inclusion criteria. Most of them reported cost information only. Data on

cost-effectiveness were presented in eight studies, only one of which incorporated an economic model. There is a paucity of evidence on most of the considered decision problems. While there exists a wealth of information regarding the costs and some information on cost-effectiveness of allogeneic SCT in adults with AML (DPs 1 and 2), there is very limited evidence on relative costs and cost-effectiveness of different techniques of SCT against further chemotherapy for other decision problems (DPs 3–8).

There is little evidence on the costs and cost-effectiveness of transplantations using different sources of stem cells (DP9) and different conditioning regimens (DP10), with the exception of some indications on costs of BMT being greater than that for PBSCT, and similarly high costs for myeloablative and non-myeloablative regimens in AML. There is no published study comparing the costs and cost-effectiveness of purging versus no purging (DP11) and of T-cell depletion versus no depletion (DP12).

Conclusions

This report provides an overview of the best available evidence on the use of SCT in the treatment of acute leukaemia. Our review demonstrated substantial differences in methodologies and coverage of evidence between existing systematic reviews/meta-analyses addressing the same decision problems. Areas in which new evidence has accumulated or is emerging have been identified. Existing evidence from DvND studies suggests that sibling donor allogeneic SCT may be more effective compared with chemotherapy in adult AML (except in good-risk patients) in CR1, childhood AML in CR1 and adult ALL in CR1, although whether the effectiveness of allogeneic SCT varies between commonly defined risk groups remains uncertain in the last two patient populations. Overall, evidence from RCTs suggested that autologous SCT is of similar effectiveness to or less effective than chemotherapy. Further RCTs and/or DvND studies are needed to evaluate the effectiveness of allogeneic and autologous SCT for adult and childhood AML and ALL in CR2+, to compare bone marrow versus cord blood transplantation and T-cell-depleted versus T-cell-replete allogeneic SCT, and to make comparisons between different myeloablative conditioning regimens.

An appreciable volume of cost studies and limited cost-effectiveness studies exists, but no firm conclusions regarding the cost-effectiveness of SCT in the UK NHS can be drawn from it owing to the methods and applicability (partly related to the age and country of origin of these studies) and significant uncertainty in the effectiveness estimates used. There is a paucity of information regarding the impact of the treatments on patients' quality of life as well as information on health service use and costs associated with SCT from the perspective of the NHS. Future research should collect reliable information on these, and then incorporate robust evidence from more recent RCTs/DvND studies to carry out economic evaluations in clearly specified patient populations. The aforementioned areas in which sufficient clinical evidence supports the use of SCT should be considered as the priority.

Publication

Ashfaq K, Yahaya I, Hyde C, Andronis L, Barton P, Bayliss S, *et al.* Clinical effectiveness and cost-effectiveness of stem cell transplantation in the management of acute leukaemia: a systematic review. *Health Technol Assess* 2010;**14**(54).

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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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.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/07/01. The contractual start date was in November 2008. The draft report began editorial review in September 2009 and was accepted for publication in March 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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