Health Technology Assessment 1998; Vol. 2: No. 8 (Executive summary)

Review

Executive summary

Bone marrow and peripheral blood stem cell transplantation for malignancy

PWM Johnson[1]
SJ Simnett[2]
JW Sweetenham[3]
GJ Morgan[4]
LA Stewart[2]

1 ICRF Cancer Medicine Research Unit, St James's University Hospital, Leeds
2 MRC Cancer Trials Office, Cambridge
3 CRC Wessex Regional Medical Oncology Unit, Southampton General Hospital
4 University of Leeds

Health Technology Assessment
NHS R&D HTA Programme

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.

Publication

Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA. Bone marrow and peripheral blood stem cell transplantation for malignancy. *Health Technol Assessment* 1998;**2**(8).

NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

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.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 1703 595 639 Email: hta@soton.ac.uk
http://www.soton.ac.uk/~hta

ISSN 1366-5278