To the Editor:

The role of unrelated donor bone marrow transplantation (BMT) in the treatment of leukemia has been an area of controversy for some years. Although there has never been any doubt that occasional patients are cured by this procedure, sometimes at advanced stages of their disease, the place of such transplants in the routine management of children and adults with leukemia has not been defined clearly. To address the current problems in this area and to identify, if possible, areas of future development, a Consensus Conference was organized. This conference brought together experts in the management of leukemia, using both conventional and transplantation techniques in adults and children, health economics, and medical ethics. New concepts such as the use of umbilical cord blood cells and immunotherapy were also addressed.

A panel, under the chairmanship of Prof E.C. Gordon-Smith (St George’s Hospital, London, UK) was convened to hear the presentations and to prepare a consensus statement. The panel members (see below) included an expert in BMT, a general hematologist, a pediatrician, patient advocates, and a medical journalist. The panel was asked to consider, if possible, four questions about unrelated donor BMT. These were to identify the current indications for such transplants in adults and children, to consider what was appropriate in terms of donor care, and to consider what studies might contribute to improved evaluation of the procedure. In addition to the presentations given at the conference, the panel also had received in advance the four background papers published subsequently in Blood Reviews. These papers were sent to referees for comment and were amended in the light of these comments before being distributed to the panel members.

During the 2-day conference, the Consensus Panel produced the Consensus Statement, which follows. In addition to making recommendations about how published reports on unrelated donor BMT should present results, the statement makes strong recommendations with regard to the introduction of molecular typing at both HLA class I and II to ensure optimal matching between donor and recipient and, in addition, proposes that current differences be removed between the management of family and unrelated donors with regard to the use of hemopoietic growth factor mobilized peripheral blood stem cells (PBSC).

Consensus Conference on Unrelated Donor Bone Marrow Transplantation: Royal College of Physicians of Edinburgh, October 29th and 30th, 1996

CONSENSUS CONFERENCE ON UNRELATED DONOR BMT

OCTOBER 29-30, 1996

Its Use in Leukemias and Allied Disorders

BMTs from unrelated donors for leukemias are increasing greatly in number and also in proportion to matched sibling donor transplants. The panel has considered unrelated donor transplant (UD-BMT) on the basis of efficacy, toxicity, and indications in leukemias. The conclusions and statements are based largely but not exclusively on information provided at the Consensus Conference.

Efficacy

(1) Unrelated BMTs for some types of leukemia can produce prolonged quiescence and, in some cases, eradication of disease.

(2) Data based on serologically matched donors at HLA A,B and DR suggest that matched unrelated transplants may have similar survival to sibling transplants in comparable disease states. This is accepted as a reasonable statement but begs the question of what is implied by matched in unrelated transplants. Much of the data concerning the survival and toxicity in unrelated transplants have come from studies using serologic typing. The effect of molecular typing on outcome may alter indications.

(3) Information on the place of sibling transplants compared with chemotherapy and autologous transplants in the management of some leukemias has been provided by randomized studies organized by the EORTC and the MRC. These studies define the place of sibling BMT in the management of acute leukemias. Conclusions drawn from these studies on the presence or absence of benefit of sibling transplants may apply to unrelated transplants.

(4) In a few situations, the evidence for efficacy is based on the level 1 documentation of zero survival after conventional therapy but with some survivors after transplant (eg, childhood acute lymphoblastic leukemia [ALL] with early bone marrow relapse). However, in situations in which alternative therapies occasionally succeed, level 1 evidence from randomized trials is rarely available to help in decision making.

(5) There is variation in outcome reported from different sources for particular conditions. In part, this may be because subdivisions of different types of leukemia are not always accurately defined.

REFERENCES

1. Aplan PD, Chervinsky DS, Stanulla M, Burhans WC: Site-specific DNA cleavage within the MLL breakpoint cluster region induced by Topoisomerase II inhibitors. Blood 87:2649, 1996


Attempts to identify subgroups and to compare like with like are essential, even though they may make data collection and comparisons more arduous. (6) It is important that rigorous economic evaluations and quality of life studies are performed alongside like with like comparisons.

**Toxicity**

(1) Increasing age and degree of mismatch each increase the probability of transplant-related mortality and morbidity and need to be taken into account when assessing the use of UD-BMT in any situation. In young (<20 years) good-risk patients, the mortality of the procedure is of the order of 15%, which increases in older patients (at 45 years to 30% or more).

(2) Transplants with an HLA-mismatched (A,B or DR) marrow have a high toxicity compared with matched marrow and cannot be equated with sibling transplants.

(3) There are, to date, few published studies concerning quality of life in recipients of UD-BMT. To inform decision making, such information must be collected using well-validated standardized tests.

**Indications**

(1) Information that allows the classification of various diseases into good, standard, and high risk is essential in allowing comparative assessment of treatments including UD-BMT.

(2) Evidence suggests that the results of UD-BMT are better when performed early in some diseases. However, the timing of UD-BMT depends on the consideration of other treatment options.

(3) For patients with chronic myelogenous leukemia (CML) in chronic phase or accelerated phase, UD-BMT should be considered as the best available treatment at present for patients without a matched sibling donor, providing that the unrelated donor provides a close match (level 1c evidence).

(4) For patients with acute myelogenous leukemia (AML) in first remission, UD-BMT has little place at the present time. In second complete remission, it may be considered, although its role in relation to other therapies requires further evaluation. UD-BMT has a clear place in a subgroup of patients with initial refractory disease, secondary AML, and high risk myelodysplastic syndromes (level 1c evidence).

(5) For a small group of children with very high-risk ALL in first remission and for children in second remission who have sustained an early bone marrow relapse, data suggest that survival may be improved by UD-BMT (level 1c evidence). Similar criteria may apply to adult ALL, but present data are even more limited.

(6) The results of UD-BMT for desperate disease (such as CML in blast crisis or acute leukemia in overt relapse) are discouraging (10% or less survival) and are associated with marked and often unquantitated toxicity. It may be considered that toxicity inflicted on the unsuccessful recipients negates the slim chance of benefit to those where the treatment is successful in terms of survival.

**Information for Decision Making**

(1) UD-BMT should only be performed where there are facilities for full characterization of the recipient’s disease, molecular HLA typing, and guaranteed reporting to national or international registries.

(2) For conditions in which there is no level 1 evidence and there is doubt about the benefits of UD-BMT versus other therapies, the procedure is only justified as part of a randomized trial (or formal pilot for such a trial).

(3) With respect to more general planning of services, it is important to research the issue of whether UD-BMT should take place in a limited number of specialized units.

**The Donors**

(1) PBSC collection has potential advantages compared with collection of bone marrow under general anesthetic. However, there are uncertainties concerning short-term and long-term toxicity of using granulocyte colony-stimulating factor with PBSC. This is inevitable because of the small numbers that have been performed in healthy donors. It would seem reasonable to offer to volunteer donors the alternative of PBSC collection, emphasizing the uncertainties, but only where properly informed consent is possible and agreed standardized protocols are followed that include systematic long-term follow-up of the donors.

(2) Policies on anonymity differ widely throughout the world. There are good reasons to maintain strict anonymity between donor and recipient despite theoretical problems in donor recruitment. The potential problems of breaking this anonymity seem to outweigh the benefits of disclosure. Systematic investigation of these matters should be performed.

(3) Further research addressing the complex ethical and psychosocial issues surrounding related and unrelated donors should be undertaken.

**CONSENSUS PANEL**

Dr Corinne Camilleri-Ferrante (Consultant in Public Health Medicine, Director Anglia Clinical Audit and Effectiveness Team); Prof Cam Donaldson (Professor of Health Economics, University of Aberdeen); Prof Ted Gordon-Smith, Chairman (Professor of Haematology, St George’s Hospital Medical School, London); Dr Lesley Falwell (Reader in Psycho-Oncology, Department of Oncology, University College London Medical School); Prof Alois Gratwohl (Division of Haematology, Department of Internal Medicine, Kantonsspital Basel, Switzerland); Prof Roy Meadow, Vice-Chairman (President, College of Paediatrics and Child Health and Professor of Paediatrics and Child Health, St James’s University Hospital, Leeds); Becky Miles (Regional Cancer Adviser, NHS Executive and Chair National Cancer Alliance); Dr Donald J. Moir (Consultant in Haematology, Milton Keynes General Hospital, Milton Keynes); Prof David Sackett (Director, NHS R&D Centre for Evidence-Based Medicine, Oxford); and Geoffrey Watts (Presenter of Medicine Now, BBC Radio 4).

**INVITED PARTICIPANTS**

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ORGANIZING COMMITTEE

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