A meta-analysis of unrelated donor umbilical cord blood transplantation versus unrelated donor bone marrow transplantation in adult and pediatric patients

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CRD summary
This review concluded that, despite greater donor-recipient human leukocyte antigen disparity, unrelated donor cord blood transplantation has consistently equivalent survival outcomes in both children and adults with malignant and non-malignant disorders compared with unrelated donor bone marrow transplantation. However, the suggestion of significant statistical and possibly clinical variability suggests that the authors' conclusions may not be reliable.

Authors' objectives
To compare the effects of unrelated donor cord blood transplantation (UCBT) versus unrelated donor bone marrow transplantation (UBMT) in adults and children with malignant and non-malignant disorders.

Searching
MEDLINE, EMBASE, the Cochrane CENTRAL Register (Cochrane Library, Issue 1, 2006), the Cochrane Database of Systematic Reviews, ACP Journal Club and DARE were searched up to January 2006; the search terms were reported. The following collections of abstracts were handsearched up to January 2006: the American Society of Hematology, the International Bone Marrow Transplant Registry, the American Society of Blood and Marrow Transplantation, and the European Society of Bone Marrow Transplant Meetings. In addition, the reference lists of retrieved articles were checked. Only full-text articles were included.

Study selection
Study designs of evaluations included in the review
Comparative clinical trials were eligible for inclusion. Randomised clinical trials were initially sought but none were found, so the review was expanded to include other clinical trial designs.

Specific interventions included in the review
Studies comparing UCBT and UBMT were eligible for inclusion. Only comparisons between fully-matched human leukocyte antigen (HLA) UBMT (6/6 match) and 0 to 2 antigen-mismatched UCBTs were included in the analysis, with the exception of one study where mismatched UBMT could not be analysed separately. T-cell depleted UBMT were not eligible for inclusion. Two studies evaluated 100% HLA-matched transplants; in the remaining studies the percentage of fully-matched transplants ranged from 0 to 87%.

Participants included in the review
Adults and children with malignant or non-malignant disorders requiring allogeneic haematopoietic stem cell transplants were eligible for inclusion. Studies without groups of demographically comparable patients were excluded from the review. Where stated, the median age of the included participants ranged from 4.5 to 36 years and the ratio of males to females from 1.04 to 2.11. Two studies included participants with acute leukaemia, two with haematological malignancies and two with haematological diseases.

Outcomes assessed in the review
The primary outcome of interest was survival. The secondary outcomes included engraftment, graft-versus-host disease (GVHD), transplantation-related mortality (TRM) and relapse. All of the included studies reported overall survival, recurrence-free survival/disease-free survival, in addition to white cell and platelet engraftment, GVHD and TRM.

How were decisions on the relevance of primary studies made?
Three reviewers independently assessed the eligibility of the studies. Any disagreements were referred to a statistician.
Assessment of study quality
The consistency, accuracy and comparability of treatment group characteristics were assessed; no further details were reported. The authors did not state how many reviewers performed the validity assessment, or how any disagreements were resolved.

Data extraction
Three reviewers independently extracted the data using a standardised data extraction form. Any disagreements were resolved through consultation with a statistician. Study authors were contacted for additional or missing data. Data for neutrophil and platelet engraftment, TRM, relapse, GVHD and overall or event-free survival were extracted.

Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous data (e.g. incidence of GVHD) and hazard ratios (HRs) with 95% CIs for time-to-event data (e.g. overall mortality, disease-free survival, TRM and relapse occurring over time). If HRs were not available in the original paper they were estimated (where possible) from Kaplan-Meier curves.

Methods of synthesis
How were the studies combined?
The studies were grouped by outcome and pooled RRs or HRs, with 95% CIs, were calculated using either a fixed-effect analysis or, in the event of significant statistical heterogeneity, a random-effects analysis. Only TRM in children appears to have been pooled using a fixed-effect analysis; the other outcomes were pooled using a random-effects analysis.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic. Some clinical differences between the studies were evident from the tables and text.

Results of the review
Six studies were included in the review; three included children (n=477) and three included adults (n=1,312).

In terms of study quality, randomisation and blinding were not possible. All of the studies had minor differences in the patient characteristics of the study groups, but these were usually not significant.

Children.
Two studies showed a lower probability of white cell engraftment for UCBT at 45 days (HR 0.92, 95% CI: 0.79, 1.08; 1 study) and 60 days (HR 0.84, 95% CI: 0.76, 0.93; 1 study). Time to platelet independence or engraftment was similar for both UCBT and UBMT (HR 1.06, 95% CI: 0.97, 1.15, p=1.09; 2 studies). The risk of having early (day 100) TRM was lower with UBMT (HR 2.08, 95% CI: 1.37, 3.16, p=0.0006; 2 studies). The risk of relapse was significantly lower in patients with UCBT (HR 0.96, 95% CI: 1.12, 3.43; 1 study). There were no significant differences in overall survival at 2 years (HR 0.76, 95% CI: 0.31, 1.87, p=0.55; 2 studies) or 3 years (HR 1.95, 95% CI: 0.44, 2.54, p=0.91; 1 study). UBMT was associated with improved disease-free survival (HR 0.60, 95% CI: 0.45, 0.81; 1 study). There were no significant differences between UCBT and UBMT in GVHD grade II-IV (HR 0.96, 95% CI: 0.44, 2.09, p=0.92; 3 studies) and grade III-IV (HR 1.46, 95% CI: 0.42, 5.03, p=0.55; 3 studies); however, there was evidence of significant heterogeneity between the studies. When only chronic GVHD was assessed, rates were significantly lower with UCBT (HR 0.26, 95% CI: 0.12, 0.57, p=0.0007; 2 studies).

Adults.
The risk of experiencing a relapse (HR 0.86, 95% CI: 0.62, 1.19, p=0.36; 3 studies) and early TRM (HR 1.04, 95% CI: 0.52, 2.08, p=0.91; 3 studies) was the same in the UCBT and UBMT groups. Studies assessing overall survival could not be pooled, but 2 studies showed a significant difference in favour of UBMT. No significant differences were observed between UCBT and UBMT for disease-free survival (HR 1.56, 95% CI: 0.76, 3.17, p=0.23; 3 studies); however, there was evidence of significant heterogeneity between the studies. UBMT was shown to be consistently better than UCBT.
for white cell engraftment (2 studies) and also for platelet engraftment (2 studies), but the studies could not be pooled in either instance. Acute GVHD was less in UCBT (2 studies), but again the studies could not be pooled.

Authors' conclusions
UCBT, despite greater donor-recipient HLA disparity, has consistently equivalent survival outcomes in both children and adults compared with UBMT.

CRD commentary
This review was based on a clearly defined review question. An adequate search was carried out for both published and unpublished data, with no language restrictions reported, and so the risk of publication and language bias appears low. In addition, three reviewers assessed the eligibility of studies and extracted the data, which reduces the risk of errors and bias. Study validity was assessed, but the criteria used and the findings for each individual study were not reported clearly. It was also unclear whether appropriate steps were taken to reduce the risk of error and bias when performing the quality assessment so, overall, it is difficult to assess the reliability of the data.

The majority of the pooled effect sizes appear to show significant statistical heterogeneity, although the power of the statistical test used (I-squared) is likely to be poor given the small number of included studies. Nevertheless, the suggestion of significant heterogeneity and the apparent clinical differences between studies suggest that the authors' conclusions may not be reliable and should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that where patients do not have an optimally matched bone marrow donor readily available (especially where an urgent transplantation is required), and even for patients with potentially unrelated donors, 1 or 2 antigen-mismatched UCBT is a viable and equally effective alternative for patients needing a matched donor UBMT.

Research: The authors did not state any implications for further research.

Bibliographic details

PubMedID
17382250

DOI
10.1016/j.bbmt.2006.11.005

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Bone Marrow Transplantation /adverse effects; Child; Child, Preschool; Clinical Trials as Topic; Cord Blood Stem Cell Transplantation /adverse effects; Disease-Free Survival; Graft Survival; Graft vs Host Disease; Hematopoietic Stem Cell Transplantation /adverse effects; Humans; Middle Aged; Neoplasms /therapy; Transplantation, Homologous /adverse effects

AccessionNumber
12007001220

Date bibliographic record published
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.