Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: a meta-analysis

Authors' objectives
The authors' objective appears to be to review and summarise the published evidence comparing the incidence of acute and chronic graft-versus-host disease (GVHD) and malignant relapse following peripheral blood stem cell transplantation (PBSCT), with that following bone marrow transplantation (BMT).

Searching
MEDLINE, Cancerlit, and the Cochrane Library were searched using the broad categories of 'bone marrow transplantation', 'hematopoietic stem-cell transplantation' and 'bone marrow purging'. The search strategy was then narrowed using Boolean combinations of the following keywords: 'allogeneic', 'graft-versus-host disease', 'stem cell', 'clinical' and 'malignant'. The reference lists of all identified articles, as well as those of review articles and meta-analyses, were reviewed for other relevant articles.

Study selection
Study designs of evaluations included in the review
Randomised trials, cohort studies and case-control studies were included in the review. Review articles and other meta-analyses were excluded.

Specific interventions included in the review
Studies comparing PBSCT and BMT were included in the review.

Studies were excluded if they were trials of GVHD prophylaxis, or if they examined methods of GVHD prevention by either positive (CD34+ selection) or negative (T-cell depletion) selection of stem cells.

Participants included in the review
Studies of malignant disease in humans were included.

Outcomes assessed in the review
Studies with GVHD as a clinical outcome were included, whereas relapse-monitoring studies were excluded. The primary outcomes were acute and chronic GVHD, and the secondary outcome was relapse rates.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data onto pre-printed data extraction forms. The extracted data included:

an assessment of demographic variables, i.e. age, gender, indications for transplant, and GVHD prophylaxis;

transplant graft characteristics, in terms of CD34+ and CD3+ doses; and

the outcome variables, i.e. incidence and severity of acute and chronic GVHD, short- and long-term mortality, and
relapse rates.

The extracted data were collected by one author, who also reviewed the manuscripts when discrepancies in the data extraction arose. An attempt was made to contact all primary authors for missing or incomplete information.

**Methods of synthesis**

How were the studies combined?
The data were combined by a meta-analysis, which used both a fixed-effect model and the random-effects model of DerSimonian and Laird (see Other Publications of related Interest no.1) to obtain a pooled effect estimate of the relative risks (RRs) for acute and chronic GVHD, along with 95% confidence intervals (CIs).

Meta-regression analyses were used to either explore heterogeneity in the included studies or to test a clinical hypothesis. A meta-regression model with two covariates (stem cell source and the difference of the T-cell doses delivered) was developed to explore the differences between the PBSCT and BMT groups.

Adjusted rank correlation tests and asymmetry tests (see Other Publications of Related Interest nos.2-3) were used to assess any impact of publication bias on the reported outcomes. In addition, graphical funnel plots were generated to enable a visual inspection for publication bias.

**How were differences between studies investigated?**

Inter-study heterogeneity was assessed using the Q statistic and by the subsequent generation of a Cochran chi-squared value. Where appropriate, sensitivity analyses were undertaken to explore significant inter-study heterogeneity.

**Results of the review**

A total of 16 studies with 2,144 participants were included in the meta-analysis: 4 randomised trials (n=660), 1 non-randomised trial (n=39), 6 cohort studies (n=289) using historical controls, and 5 retrospective cohort studies (n=1,156). The numbers of participants in each of the PBSCT and BMT groups were not reported.

Fifteen studies, including 5 randomised trials and 10 cohort studies, reported the incidence of acute GVHD. There was an increased risk of acute GVHD, after PBSCT compared with BMT; the RR using the random-effects model was 1.16 (95% CI: 1.04, 1.28, p=0.006). This estimate was equivalent to that obtained using the fixed-effect model, because of extremely low heterogeneity between the studies (Q=8.65, d.f.=14, p=0.85). Restricting the analysis to randomised trials did not affect this result. Data regarding the severity of GVHD was available for 10 studies. This showed no significant difference between the two graft types; the RR for severe acute GVHD (grade 3 to 4) after PBSCT, compared with BMT, was 0.99 (95% CI: 0.79, 1.24).

Fourteen studies, including 5 randomised trials and 9 cohort studies, reported the incidence of chronic GVHD. There was an increased risk of chronic GVHD after PBSCT, compared with BMT; the RR using the random-effects model was 1.53 (95% CI: 1.25, 1.88, p<0.001). This estimate had a moderate amount of heterogeneity (Q=42.38, d.f.=13, p<0.001). Restricting the analysis to randomised trials did not affect this result. Twelve studies reported the incidence of clinically extended versus limited chronic GVHD. There was an increased risk of clinically extensive chronic GVHD after PBSCT, compared with BMT; the RR using the random-effects model was 1.66 (95% CI: 1.35, 2.05, p<0.001). Data from one large, retrospective database review were excluded from this analysis.

In the meta-regression model, the RR of chronic GVHD increased as the difference in T-cells delivered between the PBSCT and BMT grafts increased. However, this relationship did not reach statistical significance.

Eleven studies reported the rates of relapse after PBSCT or BMT. Failure of remission induction and early progression were considered as relapses, regardless of when they were diagnosed after transplantation. There was no statistically significant difference, in terms of prevention of recurrence, between the two graft types; the RR after PBSCT, compared with BMT, was 0.81 (95% CI: 0.62, 1.05).

**Authors' conclusions**
Both acute and chronic GVHD were more common after PBSCT than BMT; this may be associated with lower rates of malignant relapse. The magnitude of the transfused T-cell load may explain the differences in chronic GVHD risk.

CRD commentary
The review question was clearly defined in terms of the intervention, outcome measure and study design. The description of the literature search was incomplete, though the search appeared comprehensive. No attempt to identify unpublished research was described; however, no significant evidence of publication bias was found.

The authors did not report any method of assessing the methodological quality of the included trials, or the potential impact of bias introduced by methodological flaws in the primary studies. These factors should be considered when interpreting the findings of this review.

The authors stated that demographic data on the study participants, and details of the study designs, were extracted from included studies. However, these data were not reported in the review. It was, therefore, difficult to ascertain the specific groups of patients to which the findings of this review could be applied. The statistical methods used to combine the data from individual studies, and to investigate potential factors affecting the pooled effect, were appropriate. However, the reported use of a fixed-effect model for the meta-analysis, in addition to the random-effects model, may be considered superfluous since the results of these analyses were not reported and no conclusions were drawn from them.

The results of the heterogeneity tests were not always reported. The conclusions regarding the increased risk of acute and chronic GVHD after PBSCT, compared with BMT, followed from the results of the review as reported. The implied link between PBSCT and lower rates of malignant relapse, as well as the association between magnitude of T-cell load and differences in chronic GVHD risk between graft types, were based upon findings which did not reach statistical significance; these should, therefore, be viewed with caution.

Implications of the review for practice and research
Practice: The authors state that the results of their analysis, as well as those of the forthcoming publications, need to be considered strongly when choosing allogeneic stem cell sources with patients before matched sibling transplantation. Allogeneic PBSCT seems to be associated with a greater degree of acute and chronic GVHD than BMT, although this may be in conjunction with lower rates of relapse. Whether this increase in GVHD and decrease in relapse results in significant changes in early or late mortality is not yet evident. The ramifications of improved GVHD prophylaxis, the impact of T-cell depletion of peripheral blood stem cell grafts on the incidence rates of GVHD, and ultimately, the choice of the most appropriate stem cell graft, remain to be seen.

Research: The authors state that it will be important to include measures of the cost and quality of life in future comparative trials.

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Other publications of related interest

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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.