Individual patient data meta-analysis of allogeneic peripheral blood stem cell transplant vs bone marrow transplant in the management of hematological malignancies: indirect assessment of the effect of day 11 methotrexate administration

Bensinger W

CRD summary
This individual patient data meta-analysis found that overall survival was significantly better and rates of relapse and relapse-related deaths were significantly lower for patients prescribed four-dose methotrexate and who received allogeneic peripheral blood stem cell transplants compared to bone marrow transplants. This project was conducted by a collaborative meta-analysis group and the conclusions seem reliable.

Authors' objectives
To evaluate the effect of day 11 methotrexate on human leukocyte antigen-matched (HLA-matched), related allogeneic peripheral blood stem cell (PBSC) transplants and bone marrow transplants for the treatment of haematological malignancies.

Searching
MEDLINE, EMBASE, LILACS, CANCERLIT and The Cochrane Library were searched without language restriction from 1990 to 2002. Search terms were reported (Other Publications of Related Interest 1). Relevant conference abstracts were also searched and experts in the field contacted for additional data. Periodic searches were also performed up to August 2003 (Other Publications of Related Interest 2).

Study selection
Randomised controlled trials (RCTs) of PBSC transplants in comparison with bone marrow for the treatment of adult patients with haematologic malignancies and HLA-matched sibling donors were eligible for inclusion.(Other Publications of Related Interest 2).

The included participants were treated with graft-versus-host-disease (GVHD) prophylaxis of methotrexate (MTX) and cyclosporine (CSA) of either three or four doses. Dosage of methotrexate was 15mg/kg at day one and 10mg/kg for the remaining days. Patients were initially given intravenous cyclosporine at a dose ranging from 2mg/kg to 5mg/kg and a subsequent switch to oral administration, depending on blood levels. Most donors in the included studies were matched siblings. The age of participants in the included studies ranged from seven years to 65 years. The proportion of males ranged from 52.5% to 74.3%. Participants in the included studies were diagnosed with various haematological malignancies, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS). Some patients had also undergone total-body irradiation (TBI). Participants also received granulocyte colony-stimulating-factor (G-CSF) for PBSC mobilisations using Filgrastim (10μg/kg four or five times daily) or Lenograstim (10μg/kg four or five times daily). The outcomes included in the review were overall survival, relapse or progression, GVHD, disease-free survival, death in remission and engraftment.

The authors stated neither how studies were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Data were checked for inconsistencies and trial investigators were contacted to resolve any discrepancies. Raw data were also checked against the results of the trial publications. Checks for imbalances between the randomised groups, differences in accrual, length of follow up and any differences in the numbers in subgroups were also performed.

Data extraction
Principal investigators of identified studies were contacted and provided updated individual patient data. Data on time to neutrophil and platelet engraftment, date of relapse or disease progression, date of onset and grade of acute GVHD and chronic GVHD, and date of last follow-up or death were extracted for each individual patient. Time was calculated from the date of randomisation, except for acute GVHD (where it was from the date of the transplant) and chronic...
GVHD (where it was 100 days after the transplant). Data on patients were separated into separate categories for early stage and late stage disease, by consensus of all reviewers.

**Methods of synthesis**
The individual log-rank statistics were combined to provide an overall estimate of the effect of PBSC compared to bone marrow for the outcomes of interest. Odds ratios were calculated together with corresponding 95% confidence intervals (CI). Comparisons were based on an intention-to-treat analysis. Statistical heterogeneity was assessed using the Chi² test. Subgroup analyses were performed to compare patients who were given four doses of methotrexate with those receiving three doses, by fitting an interaction term in the model.

**Results of the review**
Individual patient data from nine RCTs (n=1,107) were included in the analyses: six RCTs (n=573) assessed four doses of methotrexate and three RCTs (n=534) evaluated three doses of methotrexate.

**Survival and disease-free survival**: Overall survival was significantly better for patients prescribed four dose methotrexate who received PBSC compared to bone marrow (odds ratio 0.67, 95% CI: 0.52 to 0.88, p=0.004). There were no significant differences in overall survival between PBSC and bone marrow in patients prescribed three-dose methotrexate. There was a significant improvement in disease-free survival for those who received four-dose methotrexate and PBSC compared to bone marrow (odds ratio 0.62, 95% CI: 0.48 to 0.80, p=0.00023). Improvement in disease-free survival with four-dose methotrexate and PBSC was seen in patients with both early stage disease and late stage disease. There were no significant differences in disease-free survival between patients treated with PBSC or bone marrow among those who received three-dose MTX.

**Mortality with or without relapse**: Mortality due to relapse was higher in patients prescribed four doses of methotrexate who received bone marrow compared to PBSC (24% versus 14%, odds ratio 0.58, 95% CI: 0.37 to 0.91, p=0.018). There were no significant differences for mortality due to relapse rates for patients treated with PBSC or bone marrow and who were prescribed three doses of methotrexate. For patients prescribed four doses of methotrexate, non-relapse mortality was 31% in PBSC recipients compared to 36% in bone marrow recipients (p=0.06). Among patients prescribed three doses of methotrexate, non-relapse mortality was 35% in PBSC recipients and 26% among bone marrow recipients (p=0.057). For patients prescribed four doses of methotrexate, relapse at six years was 19% in PBSC patients compared with 37% in bone marrow patients (p=0.0015). For patients prescribed three doses of methotrexate there were no significant differences for relapse rates between PBSC and bone marrow recipients (27% for both).

**Acute or chronic GVHD**: There were no statistically significant differences in the risks of acute GVHD grades II to IV for recipients of either PBSC or bone marrow, regardless of whether patients were prescribed three or four doses of methotrexate. Overall, 40% of patients developed grade II to IV and 30% developed grade III to IV acute GVHD. There was a significant increase in the risk of patients developing chronic GVHD (extensive and any state) treated with PBSC, regardless of whether patients were prescribed four doses of methotrexate at any stage (odds ratio 1.43, 95% CI: 1.51 to 3.23, p<0.016) or three doses of methotrexate at any stage (odds ratio 1.96, 95% CI: 1.45 to 2.65, p<0.00001).

PBSC was associated with earlier neutrophil engraftment compared to bone marrow irrespective of whether three or four doses of methotrexate were prescribed.

**Authors’ conclusions**
The review found that overall survival was significantly better for patients prescribed four-dose methotrexate and who received PBSC compared to bone marrow. However, there were no significant differences in overall survival between PBSC and bone marrow in patients prescribed three doses of methotrexate. There was a significantly lower rate of relapse and relapse-related deaths among patients who received PBSC and four doses of methotrexate. There were no statistically significant differences in rates of transplant-related deaths among patients receiving PBSC or bone marrow regardless of whether three or four doses of methotrexate were prescribed.

**CRD commentary**
The review addressed a clear question defined in terms of intervention, comparator, participants, outcomes and study.
design. Several relevant sources were searched. Efforts were made to reduce language bias. Some efforts were made to locate unpublished data. A collaborative group of trial investigators was established to maximise retrieval of the individual patient data and to review results and conduct the meta-analysis. Methods used to select studies were not described, so it was unknown whether efforts were made to reduce reviewer errors and biases. Full details of the analysis methods were not reported (for example, whether the studies combined using a fixed- or random-effects model, or a stratified log-rank analysis). All the results were reported as odds ratios, rather than hazard ratios, which appeared to contradict the analysis methods. This project was conducted by a collaborative meta-analysis group and the conclusions seem reliable.

Implications of the review for practice and research

Practice: The authors did not state any recommendations for practice.

Research: The authors stated that further randomised controlled trials were needed to compare three or four doses of methotrexate with cyclosporin in recipients of allogeneic PBSC or bone marrow.

Funding


Bibliographic details

Bensinger W. Individual patient data meta-analysis of allogeneic peripheral blood stem cell transplant vs bone marrow transplant in the management of hematological malignancies: indirect assessment of the effect of day 11 methotrexate administration. Bone Marrow Transplantation 2006; 38(8): 539-546

PubMedID

16953207

DOI

10.1038/sj.bmt.1705488

Original Paper URL

http://www.nature.com/bmt/journal/v38/n8/abs/1705488a.html

Other publications of related interest


Indexing Status

Subject indexing assigned by NLM

MeSH

Bone Marrow Transplantation /adverse effects /methods /mortality /statistics & numerical data; Disease Management; Dose-Response Relationship, Drug; Graft vs Host Disease /drug therapy /prevention & control; Hematologic Neoplasms /complications /mortality /therapy; Humans; Immunosuppressive Agents /administration & dosage; Methotrexate /administration & dosage; Odds Ratio; Peripheral Blood Stem Cell Transplantation /adverse effects /methods /mortality /statistics & numerical data; Randomized Controlled Trials as Topic; Recurrence; Survival Analysis; Time Factors; Transplantation, Homologous
AccessionNumber
12006007549

Date bibliographic record published
03/11/2008

Date abstract record published
26/08/2009

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.