Total body irradiation plus cyclophosphamide versus busulphan with cyclophosphamide as conditioning regimen for patients with leukemia undergoing allogeneic stem cell transplantation: a meta-analysis
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CRD summary
The review found that outcomes after allogeneic stem cell transplantation for patients with leukaemia differed according to the conditioning regimen used and the type of leukaemia. Although the review was limited by the small amount of data, variation between studies, lack of randomised evidence and poor reporting of study characteristics, the authors’ cautious conclusion appears likely to be reliable.

Authors’ objectives
To compare the efficacy of total body irradiation plus cyclophosphamide versus busulphan plus cyclophosphamide as conditioning regimens for patients with leukaemia undergoing allogeneic stem cell transplantation.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Center for International Blood and Marrow Transplant Research (CIBMTR) databases were searched from 1990 to April 2009, with no apparent language restrictions. Search terms were reported. Abstracts of conference proceedings and the reference lists of articles retrieved were also checked.

Study selection
Controlled studies that compared total body irradiation plus cyclophosphamide versus busulphan plus cyclophosphamide as conditioning regimens for patients with leukaemia undergoing allogeneic stem cell transplantation were eligible for inclusion. Stem cells in eligible studies could be derived from related or unrelated, matched or mismatched donors, and from bone marrow or peripheral blood. Studies were required to report overall or disease-free survival (primary outcomes), neutrophil or platelet engraftment, transplant-related mortality, relapse and/or graft versus host disease. Case reports were excluded.

Participants in the review were children or adults with acute lymphoblastic leukaemia, acute myeloblastic leukaemia, or chronic myelocytic leukaemia; their ages ranged from under one year to 59 years. Previous treatment received varied across studies. Total body irradiation was given as a single dose of 7.5 to 10 Grays (Gy) or in four to six fractions with a total dose of 12 to 15Gy. In some cases a lung shield was used. Usually busulphan was given orally at 16mg/kg for four days and cyclophosphamide at 120mg/kg. Stem cells were derived from identical sibling bone marrow, peripheral blood or unrelated bone marrow. Graft-versus-host disease prophylaxis was usually cyclosporine plus methotrexate.

The authors did not state how many reviewers performed the selection.

Assessment of study quality
The following aspects of study validity were assessed: consistency, accuracy, and balance between the treatment groups (details not reported). Poor quality studies were excluded (e.g. studies without comparable demographics in the two groups).

The authors did not state how the validity assessment was performed.

Data extraction
Event rates were extracted to enable the calculation of odds ratios (ORs) with 95% confidence intervals (CIs).

Two reviewers extracted the data, with disagreements resolved by discussion.
Methods of synthesis

Studies were combined to calculate pooled odds ratios and 95% confidence intervals. Heterogeneity was assessed using the χ² and I² statistics. Fixed-effect models were used unless there was significant heterogeneity (I² over 50%), in which case random-effects models were used.

Sensitivity analyses were conducted by statistical model (fixed-effect or random-effects), and by inclusion of population-based studies only. Subgroup analyses were conducted by type of disease (acute lymphoblastic leukaemia, acute myeloblastic leukaemia or chronic myelocytic leukaemia).

Publication bias was assessed using a funnel plot and Egger regression test.

Results of the review

Eighteen studies were included in the review (n=3,172 patients, range 22 to 782); none were randomised or blinded. The demographic, disease and transplant characteristics of the two groups of participants in each study appeared comparable at baseline. Duration of follow up ranged from two to seven years.

Disease-free survival (10 studies; n=2,338 patients): Disease-free survival rates after transplantation were significantly higher in the total body irradiation plus cyclophosphamide group (OR 1.53, 95% CI 1.16 to 2.02, I²=46%), with no significant evidence of publication bias. Results differed by disease, with statistically significant benefit from total body irradiation plus cyclophosphamide for acute lymphoblastic leukaemia (OR 1.93, 95% CI 1.42 to 2.64; three studies; I²=0%) and acute myeloblastic leukaemia (OR 1.49, 95% CI 1.01 to 2.20; four studies; I²=52%), but no statistically significant difference between the treatment regimens for chronic myelocytic leukaemia (three studies).

Secondary outcomes: There was a statistically significant benefit in the total body irradiation plus cyclophosphamide treatment for: transplant-related mortality (OR 0.68, 95% CI 0.49 to 0.93; eight studies; I²=54%), veno-occlusive disease (OR 0.42, 95% CI 0.30 to 0.59; nine studies; I²=0%) and haemorrhagic cystitis (OR 0.32, 95% CI 0.19 to 0.54; four studies; I²=0%). However, total body irradiation plus cyclophosphamide was associated with a significantly higher rate of growth and development problems (OR 5.85, 95% CI 1.55 to 22.13; three studies; I²=0%), interstitial pneumonia (OR 1.70, 95% CI 1.24 to 2.32; seven studies; I²=5%) and cataract (OR 12.69, 95% CI 1.72 to 93.32; three studies; I²=65%) than busulphan plus cyclophosphamide treatment. There was no statistically significant difference between the groups in relapse rate (eight studies), graft failure (seven studies), or graft-versus-host disease. Subgroup analysis showed a significantly lower relapse rate for acute myeloblastic leukaemia in the total body irradiation plus cyclophosphamide group (three studies) and for chronic myelocytic leukaemia in the busulphan plus cyclophosphamide group (three studies).

Sensitivity analyses showed similar results to the main findings.

No significant evidence of publication bias was detected.

Authors' conclusions

Outcomes of allogeneic stem cell transplantation for patients with leukaemia differed according to the conditioning regimen used and the type of leukaemia.

CRD commentary

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for published and unpublished studies, with no apparent language restrictions. Publication bias was adequately assessed. Steps were taken to minimise the risk of reviewer error and bias by having more than one reviewer to extract data, but it was unclear how the processes of study selection and validity assessment were conducted.

Some important components of study quality were not reported (e.g. design, follow-up rate), which made it difficult to determine the reliability of the findings. Several of the forest plots in the review were incorrectly labelled with regard to the direction of effect (i.e. which intervention was favoured). Appropriate methods were used to combine the studies and assess heterogeneity. However, where significant heterogeneity was found, it was not always acknowledged or explored (e.g. the result for cataract and transplant-related mortality). The authors noted the heterogeneity of the
included studies and the potential for selection bias.

Although the review was limited by the small amount of data, variation between studies, lack of randomised evidence and poor reporting of the study characteristics, the authors’ cautious conclusion appears likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that well-powered and well-designed studies are needed on the effects of conditioning treatments, such as intravenous busulphan and reduced intensity regimens, for patients with leukaemia undergoing allogeneic stem cell transplantation.

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