Prophylaxis regimens for GVHD: systematic review and meta-analysis

CRD summary
The authors found that no prophylaxis regimen for acute graft-versus-host disease (aGVHD) investigated was superior for improving survival rates. For reducing aGVHD, methotrexate plus cyclosporine was superior to cyclosporine alone and methotrexate plus tacrolimus was superior to methotrexate plus cyclosporine. Corticosteroids were not beneficial. These conclusions are supported by the limited evidence available.

Authors' objectives
To evaluate the survival benefit of current prophylaxis regimens for acute graft versus host disease (aGVHD) among patients undergoing allogeneic stem cell transplant.

Searching
The Cochrane Library (Issue 2, 2008), PubMed (from 1966), LILACS and CancerLit were searched, as were conference proceedings of American Society of Hematology, American Society of Clinical Oncology, European Hematology Association (all from 2002) and International Society of Experimental Hematology. Search terms were reported. International and European bone marrow transplant registries, www.controlled-trials.com, ClinicalTrials.gov and references of included studies were searched. Authors of included studies were consulted. The search was not restricted by language.

Study selection
Randomised controlled trials (RCTs) of regimens considered common practice for GVHD prophylaxis were eligible for inclusion: methotrexate (MTX) regimens versus regimens without MTX; MTX plus tacrolimus versus MTX plus cyclosporine; and regimens that included steroids versus those that did not. Studies were required to include patients who underwent allogeneic bone marrow or stem cell transplant for haematological disease. Eligible studies reported outcomes for up to five years following transplantation.

The primary review outcome was all-cause mortality. Secondary outcomes included rates of grade II to IV or severe (grade IV) aGVHD at 100 days, chronic GVHD, treatment-related mortality, relapse, infection and adverse events.

All participants in the review underwent bone marrow transplant (in most cases from a matched related or unrelated donor) following myeloablative therapy for a range of haematological malignancies. Mean or median age ranged from 27 to 42 years (where stated). Included studies compared either MTX with a calcineurin inhibitor versus the calcineurin inhibitor alone, or compared various regimens with or without corticosteroids, or tacrolimus versus cyclosporine (both with MTX). Some had three comparison arms. Few studies reported infection rates. Mean duration of follow-up was 45 months (range 24 to 96 months).

Two reviewers independently selected the studies.

Assessment of study quality
Validity criteria were randomisation, allocation concealment and blinding. Two reviewers independently conducted validity assessment.

Data extraction
Risk ratios (RRs) were calculated from numbers of events in control and intervention groups of each study, with 95% confidence intervals (CIs). Intention-to-treat analysis was conducted for the primary outcome. Data for the longest follow-up point were used.

Two reviewers independently extracted the data. Disagreements were resolved by a third reviewer. Authors of primary studies were contacted for additional data.
Methods of synthesis
Studies were combined using the Mantel-Haenszel fixed-effect model to calculate pooled risk ratios and 95% CIs. Numbers needed to treat (NNT) were calculated for some outcomes. Heterogeneity was assessed by the $X^2$ test and $I^2$ statistic. A random-effects model was used if significant heterogeneity was detected ($X^2 p<0.1$ or $I^2 \geq 50\%$). Correlations between outcomes were tested using Pearson’s correlation coefficient. Subgroup analysis by donor type was conducted where there were sufficient data. Sensitivity analysis was conducted; an RCT with unbalanced groups at baseline was excluded.

Results of the review
Thirteen studies were included in the review (n=1,439, range 18 to 329). Seven studies reported adequate randomisation and allocation concealment; none were blinded.

There was no statistically significant difference in all-cause mortality between any of the regimens (12 RCTs). There was a statistically significant reduction in aGVHD associated with MTX-containing versus non-MTX-containing regimens (RR 0.49, 95% CI 0.38 to 0.65, NNT=4, 95% CI 3 to 7; six RCTs, $I^2=5\%$), but no statistically significant difference between the groups in rates of severe aGVHD.

Tacrolimus-based regimens were associated with a statistically significant reduction in aGVHD (RR 0.62, 95% CI 0.52 to 0.75; NNT=5, 95% CI: 4 to 9; three RCTs, $I^2=55\%$) and in severe aGVHD (RR 0.67, 95% CI 0.47 to 0.95; three RCTs, $I^2=0\%$) compared to cyclosporine-based regimens. However, tacrolimus-based regimens were associated with a significantly higher rate of renal failure (RR 1.20, 95% CI 1.03 to 1.39; two RCTs, $I^2=28\%$).

No significant differences in rates of chronic GVHD, treatment-related mortality or relapse rate were found between any regimens in the review. Regimens with and without corticosteroids were compared and there was no statistically significant difference between the groups for any outcome.

Authors’ conclusions
None of the prophylaxis regimens for aGVHD at the time of the review was superior for improving survival rates. For reducing aGVHD, methotrexate plus cyclosporine was superior to cyclosporine alone, and methotrexate plus tacrolimus was superior to methotrexate plus cyclosporine. Corticosteroids were not beneficial with any regimen.

CRD commentary
The objectives and inclusion criteria of the review were clear in most respects, although the restriction to interventions considered common practice meant that newer drugs were excluded. Relevant sources were searched for published and unpublished studies. No final search date was reported. Steps were taken to minimise risk of reviewer bias and error by having more than one reviewer independently select studies, assess study validity and extract data. Some relevant aspects of validity were assessed, but others (such as follow-up rates) were not reported. Appropriate statistical techniques were used to combine data and assess for heterogeneity, but where significant heterogeneity was detected it was not explored in detail. It appeared that publication bias was not assessed formally. Although the review was limited by scarcity of data and small sized included studies, the direction of effect was consistent across most analyses. The authors’ conclusions are supported by the limited evidence available.

Implications of the review for practice and research
**Practice:** The authors stated that both methotrexate combined with cyclosporine and methotrexate combined with tacrolimus were acceptable for GVHD prophylaxis after allogeneic stem cell transplant. Methotrexate combined with tacrolimus may be preferable for reducing aGVHD rates. Therapy should be tailored to individual patients.

**Research:** The authors stated that RCTs were needed to evaluate use of methotrexate with tacrolimus in different transplant settings. Newer pharmacological and biological methods should be investigated, with the aim of minimising GVHD while maintaining graft versus tumour effectiveness. The primary outcome of such studies should be all-cause mortality.

Funding
Bibliographic details

PubMedID
18997826

DOI
10.1038/bmt.2008.373

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Child; Child, Preschool; Clinical Trials as Topic; Graft vs Host Disease /prevention & control; Hematologic Diseases /therapy; Humans; Immunosuppressive Agents /therapeutic use; Methotrexate /therapeutic use; Middle Aged; Randomized Controlled Trials as Topic; Recurrence; Risk; Tacrolimus /therapeutic use; Treatment Outcome

AccessionNumber
12009105785

Date bibliographic record published
05/08/2009

Date abstract record published
31/03/2010

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.