Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis

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CRD summary
This review concluded that tandem autologous haematopoietic transplant (AHCT) in treatment of previously untreated multiple myeloma was associated with improved response rates, although survival outcomes were not improved and there were clinically significant increases in treatment-related mortality compared to single AHCT. These conclusions are probably reliable, although the limited search suggests some caution in their interpretation.

Authors' objectives
To assess the effectiveness of tandem versus single autologous haematopoietic transplant (AHCT) in patients with multiple myeloma.

Searching
MEDLINE was searched up to March 2008. Conference proceedings of four relevant professional bodies were searched for the period 1993 to 2007. References of retrieved articles were searched. Experts in the field were contacted for unpublished data. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that compared tandem with single AHCT in patients with previously untreated multiple myeloma were eligible for inclusion. Trials needed to report overall survival, event-free survival, response rates or treatment-related mortality on an intention-to-treat (ITT) basis.

Most patients (70% to 100%) in the included studies had stage II or III disease. There was limited reporting of information on the included studies.

Two reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
Studies were assessed for validity using criteria of allocation concealment, use of a priori power calculations, use of ITT analysis and reporting of losses to follow-up.

Two reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted data to permit calculation of hazard ratios (HR) and risk ratios (RR) with 95% confidence intervals (CI).

Methods of synthesis
Pooled hazard ratios and risk ratios with 95% CI were calculated using random-effects model meta-analyses. Heterogeneity between studies was assessed with $\chi^2$ and $I^2$ statistics. Publication bias was assessed by funnel plot analysis and Begg's and Egger's tests. A sensitivity analysis excluded a study that used concomitant thalidomide treatment in the single AHCT group was conducted for the outcomes with statistically significant heterogeneity. Sensitivity analyses were conducted based on whether studies were reported as full publications or in abstract and on whether sample size calculations were reported.

Results of the review
Six RCTs (n=1,803) were included in the review. Overall the studies were considered to be of good quality with adequate allocation concealment, ITT analysis and sufficient description of withdrawals and drop-outs. Median follow-
up ranged from 33 to 92 months, where reported.

There were no statistically significant differences between tandem and single AHCT in either overall survival (HR 0.94, 95% CI 0.77 to 1.14, \(X^2=0.04\); six RCTs) or event-free survival (HR 0.86, 95% CI 0.70 to 1.05, \(X^2=0.02\); six RCTs).

A sensitivity analysis that excluded a study that used concomitant thalidomide in the single AHCT group removed the statistically significant heterogeneity in both analyses and produced a statistically significant benefit of tandem AHCT in event-free survival (HR 0.79, 95% CI 0.70 to 0.89; five RCTs), but there remained no significant difference in overall survival.

There was a statistically significantly higher response rate in the tandem AHCT groups (RR 0.79, 95% CI 0.67 to 0.93; four RCTs). Treatment-related mortality was statistically significantly higher in the tandem AHCT groups (RR 1.71, 95% CI 1.05 to 2.79; five RCTs).

Results of other sensitivity analyses were reported, but did not substantially alter the findings of the analyses.

There was no evidence of publication bias.

Authors' conclusions
Tandem AHCT was associated with improved response rates, although survival outcomes were not improved and it was associated with clinically significant increases in treatment-related mortality.

CRD commentary
The review question and the inclusion criteria were clear. Although only one database was searched, other potential sources were searched and attempts were made to minimise publication and language biases; the risk of relevant studies being omitted is still increased where only one main database is searched. The authors reported that they used methods designed to reduce reviewer bias and error at all stages of the review process. Validity assessment with appropriate criteria was conducted and used to inform the synthesis. Limited information on the included studies was reported. The use of meta-analysis and the assessment and exploration of statistical and clinical or methodological heterogeneity were reasonable.

The authors' conclusions reflected the results of the review and are probably reliable, although the limited search suggests some caution in their interpretation.

Implications of the review for practice and research
Practice: The authors stated that routine use of tandem AHCT was not justified in the treatment of multiple myeloma.

Research: The authors stated that an individual patient data meta-analysis may help to identify subgroups of patients who would benefit from tandem AHCT.

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