High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials

CRD summary
This well-conducted review concluded that HDT does not improve overall survival in newly diagnosed multiple myeloma. It may improve progression-free survival, but it is also associated with increased treatment-related mortality. Significant statistical variation in the included studies suggests that the pooled findings should be treated with caution.

Authors' objectives
To assess the effects of myeloablative high-dose therapy and single autologous stem cell transplantation (HDT) compared with non-myeloablative standard-dose therapy (SDT) for multiple myeloma.

Searching
Two reviewers independently searched MEDLINE (PubMed), EMBASE and the Cochrane CENTRAL Register. Key search terms were reported although search dates were not. The reference lists of retrieved articles and relevant reviews were screened. The MEDLINE and EMBASE searches were restricted to English language articles.

Study selection
Studies were eligible for inclusion if they were prospective randomised controlled trials (RCTs) with a minimum follow-up of 2 years; evaluated HDT compared with SDT for multiple myeloma; and reported hazard ratios (HRs) for overall survival or progression-free survival on an intention-to-treat basis. HDT was defined as any myeloablative regimen with a single autologous transplant, or equivalent. SDT was defined as any non transplant option.

The included studies investigated patients with newly diagnosed multiple myeloma. Most were Durie-Salmo stage II or III and were aged 65 years or younger. A range of HDT and SDT regimens was used in the included studies.

The authors did not state how many reviewers selected studies for inclusion, but did state that the studies were reviewed independently in a structured format.

Assessment of study quality
Validity was assessed using the following criteria: single or multiple participating institutions, method of randomisation and allocation concealment, drop-out rate, crossover, study power. Methodological quality was not scored, but the findings were used in subgroup and sensitivity analyses and tests of interaction.

Two reviewers assessed validity independently. Any disagreements were resolved by consensus, with reference to the original article and contact with the authors if necessary.

Data extraction
HRs were calculated where not provided. When the same study was reported in multiple publications, the most recent data were extracted.

Two reviewers extracted the data independently onto a standardised form. Any disagreements were resolved by consensus, with reference to the original article and contact with the authors if necessary.

Methods of synthesis
HRs for overall and progression-free survival, and odds ratios (ORs) for treatment-related mortality, were pooled using a random-effects model. Statistical heterogeneity was assessed using the Q statistic. Heterogeneity was explored in
relation to: study size (by meta-regression); the effect of using adjusted or imputed HRs in estimates of overall survival (sensitivity analysis); the effect of removing each study from the analysis in estimates of overall and progression-free survival (sensitivity analysis); the use of peripheral blood stem cells (subgroup analysis); longer follow-up of 4 years or more (subgroup analysis); studies with lower crossover in the SDT arm (subgroup analysis).

The Begg funnel plot and Egger's test were used to assess the risk of publication bias.

Results of the review
Nine RCTs (n=2,411) were included in the main meta-analysis, with a further non-standard study (n=115) being included in a sensitivity analysis.

All the included studies were judged to be of a good quality.

Overall survival: the pooled HR did not indicate a significant benefit of HDT over SDT (9 RCTs; HR 0.92, 95% confidence interval, CI: 0.74, 1.13, p=0.40). However, there was significant heterogeneity in this result (Q=27.65, p<0.01) which could not be explained by study size in the meta-regression (p=0.87). Sensitivity and subgroup analyses did not alter the findings.

Progression-free survival: the pooled HR indicated a statistically significant benefit of HDT over SDT (9 RCTs; HR 0.75, 95% CI: 0.59, 0.96, p=0.02). However, there was significant heterogeneity in this result (Q=51.57, p<0.01) which could not be explained by study size in the meta-regression (p=0.56). Sensitivity and subgroup analyses did not alter the findings, although the pooled HR in the subgroup of 8 studies which preferentially used peripheral blood stem cells was borderline (HR 0.77, 95% CI: 0.59, 1.00).

Treatment-related mortality: the pooled OR indicated a statistically significant greater risk of treatment-related mortality with HDT compared with SDT (10 RCTs; OR 3.01, 95% CI: 1.64, 5.50, p<0.01). The authors also stated that this was likely to be an underestimate, owing to poor reporting in the included studies.

The results of the funnel plot and Egger's test suggested that there was no publication bias.

Authors' conclusions
Overall survival was not significantly improved by HDT in newly diagnosed multiple myeloma, whereas progression-free survival was significantly better. However, the overall risk of treatment-related mortality was also significantly increased with HDT.

CRD commentary
The review addressed a clear research question using well-defined inclusion criteria. The search terms were reported, although search dates were not. The searches were restricted to English language publications in two of the three electronic databases searched, and no attempts were made to locate unpublished data; this might have resulted in some relevant studies being missed, although tests for the presence of publication bias found none. Steps were taken to minimise bias in the review process, by having two reviewers independently carry out the searches, assess validity and extract the data. However, it is not clear whether two reviewers independently selected the studies. A relevant validity assessment was undertaken and the results of this assessment reported. The studies were pooled using appropriate methodology and reasons for statistical heterogeneity explored but, since no explanation was found for the substantial statistical heterogeneity present in the meta-analyses, the findings should be treated with some caution.

Implications of the review for practice and research
Practice: The authors stated that decisions concerning the role and timing of HDT should be made collaboratively with patients, incorporating their preferences and acknowledging uncertainty. Enrolment in clinical trials that seek to address questions about the role and timing of HDT should be encouraged.

Research: The authors stated that an updated meta-analysis of individual patient data from the 10 RCTs included in this review would yield more information. They also suggest that it will be important to prospectively evaluate the benefit of early versus late HDT with novel agents such as thalidomide.
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