Role of high-dose chemotherapy and autologous hematopoietic cell transplantation in primary systemic amyloidosis: a systematic review

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CRD summary
The authors concluded that autologous hematopoietic cell transplantation did not appear superior to conventional chemotherapy in improving overall survival in primary systemic amyloidosis; however, the evidence was weak and further research was needed. This was a generally well-conducted study. Given the poor quality of the available studies and high levels of statistical heterogeneity, the authors' caution is warranted.

Authors' objectives
To assess the effectiveness of autologous hematopoietic cell transplantation (AHCT) compared to conventional chemotherapy in patients with primary systemic (AL) amyloidosis.

Searching
MEDLINE was searched from January 1966 to March 2008. Search dates for single-arm trials were restricted to January 2001 to March 2008. Search terms were reported. Abstracts of meetings of the American Society of Hematology, European Society of Hematology and American Society of Clinical Oncology were handsearched from 2001 to 2008.

Study selection
Studies of participants with AL amyloidosis were eligible if they were randomised controlled trials (RCTs) with at least 10 participants in each arm. Studies needed to compare the effectiveness of AHCT and conventional chemotherapy. Non-randomised single-arm prospective trials with or without historical controls were also eligible. Eligible studies had to report at least one of the outcomes: overall survival; event-free survival; complete haematological response (CHR); partial haematological response; renal response; treatment-related mortality; and treatment-related morbidity. Retrospective studies were excluded.

Most included studies were of high-dose or normal melphalan in combination with autologous stem cell transplantation (ASCT) or stem cell transplantation. Some studies used an adjuvant therapy. In controlled studies, comparator conditions were oral melphalan plus oral dexamethasone, melphalan plus prednisone or a combination of vincristine adriamycin and dexamethasone (VAD). One study was of chemotherapy, peripheral blood stem cell transplantation, total body irradiation and ASCT combined. Participants were Eastern Cooperative Oncology Group, South West Cooperative Oncology Group or World Health Organisation status 0-2. Median age ranged from 51 years to 59.5 years. Most participants were male.

Two reviewers selected the studies for review in consultation with two other reviewers. Disagreements were resolved by consensus.

Assessment of study quality
The reviewers commented on aspects of methodological quality (such as randomisation, allocation concealment, withdrawals and dropouts, intention-to-treat analyses and a priori sample size calculations) and evaluated the methodological quality of the studies according to GRADE criteria. Three reviewers independently assessed the methodological quality of the trials.

Data extraction
For controlled studies, time to event and dichotomous data were extracted for each group and used to calculate odds ratios (OR) or hazard ratios (HR) for individual studies. Where time-to-event data were not available, the hazard ratio was indirectly assessed using the method of Parmar et al. For single arm studies, proportions of each outcome were extracted and transformed into a quantity using the Freeman-Tukey variant of the arcsine square root transformed proportion. Three reviewers independently extracted the data.
Methods of synthesis
For controlled studies, a pooled hazard ratio (HR), odds ratio (OR) or risk ratio (RR) with 95% confidence intervals (CI) was calculated using a random-effects model. For single arm studies, a pooled proportion was calculated as a back transform of the weighted mean of transformed proportions using a random-effects model. Statistical heterogeneity was assessed using the $I^2$ statistic.

Sensitivity analyses were conducted that excluded outliers and according to the number of centres involved, treatment regime, renal status and co-operative group scoring criteria. For one study with a zero count, three sensitivity analyses were conducted: including the study; excluding the study; and using a correction factor of 0.5. Publication bias was assessed using Begg and Mazumdar's and Egger's tests. Results were also reported for the RCT only.

Results of the review
Twelve studies were included for the review (n=1,089): one RCT (n=100); two non-randomised controlled trials (n=49); and nine single arm trials (n=940). Methodological quality of studies was generally low. For the RCT, the method of randomisation was not reported and allocation concealment was inadequate, but data were treated on intention-to-treat principles, sample-size calculations were reported and withdrawals and dropouts were adequately described. All but one of the non-randomised studies reported withdrawals and dropouts, but only three reported a priori sample size calculations.

Controlled studies (n=149): Conventional chemotherapy was superior to AHCT in overall survival (HR 1.79, 95% CI 1.11 to 2.91, p=0.018; three studies, n=149). There was no significant difference between conventional chemotherapy and AHCT in CHR, partial haematological response or renal response. AHCT was associated with a significantly higher risk of treatment-related mortality (RR 22, 95% CI 1.324 to 365.5, p=0.03; one RCT, n=100), a higher incidence of treatment-related infections (21% versus 0%; one study, n=31) and a higher rate of neutropenic fever and mucositis (100% versus 0%; one study, n=18) compared to conventional chemotherapy.

Single-arm studies (n=940): Pooled proportion was 0.35 (95% CI 0.25 to 0.46; seven studies, n=598) for mortality, 0.35 for CHR (95% CI 0.26 to 0.44; eight studies, n=864) and 0.12 for treatment-related mortality (95% CI 0.09 to 0.14; nine studies, n=678). Results for other outcomes in single-arm trials were also presented.

There was no evidence of statistically significant heterogeneity for meta-analyses of controlled trials. However, there was significant statistical heterogeneity for meta-analyses of single-arm trials ($I^2$ range=71% to 86%). Sensitivity analyses did not significantly alter the results for any outcomes other than CHR. There was no evidence of publication bias for the single-arm trials.

Authors' conclusions
AHCT did not appear to be superior to conventional chemotherapy in improving overall survival in patients with AL amyloidosis; however, the evidence was weak and further research was needed.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. Several relevant journals were searched. Only one database was searched and so relevant data may have been missed. Some attempts were made to identify unpublished data. Publication bias was assessed and no evidence was found. It was unclear whether language restrictions were imposed during the search and so language bias could not be ruled out. Appropriate steps were taken during study selection, data extraction and validity assessment processes to minimise the risk of reviewer error and bias. The validity of the included studies was assessed according to suitable criteria. The quality of the included studies was generally low and the sample sizes for many studies were small. Appropriate methods were used to combine the studies, statistical heterogeneity was assessed and potential sources of heterogeneity were investigated. This was a generally well-conducted study. Given the poor quality of the available studies and high levels of statistical heterogeneity, the authors' caution is warranted.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that further well-designed adequately-powered RCTs were needed to investigate the optimal treatment for AL amyloidosis.

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