Autologous hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission: a meta-analysis of randomized trials

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CRD summary
This review found that autologous stem-cell transplants should not be used as first-line therapy in patients with acute myeloid leukaemia who had achieved a complete first remission. The authors’ conclusions should be interpreted with caution because of methodological flaws and poor reporting of the review process.

Authors’ objectives
To compare autologous stem-cell transplant treatment with further non-myeloablative chemotherapy or no treatment in patients on complete first remission with acute myeloid leukaemia.

Searching
MEDLINE, EMBASE, The Cochrane Library, Web of Science and CNKI were searched to August 2009 for relevant published studies; search terms were reported. There were no language restrictions.

Study selection
Controlled trials where patients with acute myeloid leukaemia in first complete remission without a human leukocyte antigen-matched donor were randomly allocated to either autologous stem-cell transplantation, chemotherapy or no further treatment were eligible for inclusion. The primary outcomes were disease-free survival and overall survival. Other endpoints were transplantation-related mortality and relapse.

The included populations were adult and paediatric patients (10 to 60 years) enrolled between 1984 and 2005. Patients were treated for primary acute myeloid leukaemia; in one trial, some centres excluded patients who were treated for acute promyelocytic leukaemia. Patients with Down Syndrome, myelodysplastic syndrome, granulocytic sarcoma and chronic myelogenous leukaemia were excluded in some trials. Induction therapy, consolidation chemotherapy and conditioning regimens consisted of various chemotherapeutic agents. Doses and regimens of these treatments were not reported. The source of the stem cells in most trials were from bone marrow; other trials used cells from the peripheral blood stem.

The authors did not state how many reviewers performed study selection. They stated that the review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for meta-analyses of randomised controlled trials (RCTs).

Assessment of study quality
The authors did not state they assessed methodological quality.

Data extraction
Data were extracted to calculate relative risks (RRs) or hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). Where hazard ratios were not reported, the reviewers extracted data from Kaplan-Meier survival curves.

Methods of synthesis
Pooled hazard ratios and relative risks and 95% CIs for both were calculated using a fixed-effect model. $I^2$, $T^2$ and $X^2$ were used to assess statistical heterogeneity across the outcomes. Where statistical heterogeneity was evident, a random-effects model was used. The reviewers investigated publication bias with Egger and Begg tests and by visual appraisal of funnel plots. Time-to-event hazard ratios were used to synthesise survival data. Subgroup analyses investigated patient classification by age (paediatric and adult) and overall survival evaluated according to cytogenic risk categories of good, intermediate and poor risk.

Results of the review
Thirteen studies of 12 RCTs (n=2,808 patients) were included in the review. Median sample size was 210 patients (range 34 to 840). There were 760 paediatric patients. Where reported, 751 of 1,361 patients received their assigned treatment with autologous stem-cell transplant and 1,087 of 1,341 patients received chemotherapy or no treatment.

There were statistically significant benefits observed for patients treated with autologous stem-cell transplant compared to chemotherapy or no further treatment with a reduced risk of relapse (RR 0.78, 95% CI 0.68 to 0.90, I² =52%; 11 studies) and disease-free survival (HR 0.89, 95% CI 0.80 to 0.98, I² =26%; 13 studies). Subgroup analyses showed similar findings in adult patients for both outcomes, but the difference was not significant in children. There was evidence of statistical heterogeneity.

There were no significant differences in overall survival between the different treatment groups (11 studies). The findings remained non-significant in adult and paediatric subgroups and there was some evidence of statistical heterogeneity. There were no significant differences in overall survival defined by cytogenic risk categories.

Treatment with autologous stem-cell transplant was associated with a significantly higher risk of treatment-related mortality (RR 1.97, 95% CI 1.39 to 2.80, I² =23%; 11 studies). Subgroup analyses showed similar results in adults, but there were no significant differences in paediatric patients. Some statistical heterogeneity was observed.

Survival from relapse was significantly lower in patients who received autologous stem-cell transplant compared to control groups (HR 2.09, 95% CI 1.41 to 3.08). No statistical heterogeneity was observed for this outcome. Findings were not significantly altered when one study that showed a significant result was removed.

There was no evidence of publication bias for studies that reported disease-free survival and overall survival.

**Authors' conclusions**
The results of the review indicated that autologous stem-cell transplants should not be used as first-line therapy in patients with acute myeloid leukaemia who had achieved a complete first remission.

**CRD commentary**
The review addressed a clear question. Criteria were stipulated for inclusion of studies. Appropriate electronic databases were searched without language restrictions. Restriction of the review to published studies meant there was some risk of publication bias. The authors stated that they followed a set of guidelines for the conduct of meta-analyses, but reported no steps to minimise errors and bias in the review process. It was unclear whether intention-to-treat analyses were performed. Rates of follow-up in the included trials were not known. Methodological quality of the included trials was not assessed. This made the robustness of the results of the review difficult to judge. There were some discrepancies between the results reported in the text and those in figures and tables. The authors acknowledged substantial heterogeneity in the trials. This meant that pooling the results of the trials may not have been justified, particularly in light of the statistical heterogeneity observed across the results. The authors correctly acknowledged some of the limitations of the review, in particular the large numbers of patients who did not receive their allocated treatments.

Some methodological flaws, poor reporting of the review process and a lack of information on quality and follow-up in the trials mean that the authors conclusions should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that the hypothesis could be examined by using individual patient data from the studies.

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