Management of adult patients with acute lymphoblastic leukemia in first complete remission: systematic review and meta-analysis

Ram R, Gafter-Gvili A, Vidal L, Paul M, Ben-Bassat I, Shpilberg O, Raanani P

CRD summary
This review concluded that for adult patients with acute lymphoblastic leukaemia in first complete remission, all-cause mortality was significantly lower after allogenic stem cell transplantation than for autologous stem cell transplantation or chemotherapy. Results were significant for standard-risk patients but not for high-risk patients. Evidence limitations imply the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To evaluate the management of adult patients with acute lymphoblastic leukaemia in first complete remission.

Searching
PubMed, the Cochrane Library, CANCERLIT and LILACS, were searched to March 2009 for publications in any language; search terms were reported. Two ongoing trials databases were searched on 1 March 2009 (the MetaRegister of controlled clinical trials and the NIH Clinical Trials Registry). Conference proceedings of five haematology societies and a haematology journal were scanned for relevant abstracts from 2000 to 2007. Bibliographies of each retrieved article were handsearched. The first or corresponding authors of included trials were contacted for details of ongoing and unpublished trials.

Study selection
Randomised controlled trials (RCTs) and genetically randomised studies (patient allocation to intervention on the basis of sibling donor availability) of first post-remission therapy in adults (aged over 15 years) with acute lymphoblastic leukaemia in first complete remission, were eligible for inclusion. For trials to be eligible, patients could have standard risk or a high risk of acute lymphoblastic leukaemia.

The primary outcome was all-cause mortality at the longest available follow-up if below five years. Secondary outcomes were disease recurrence (relapse), and non-relapse mortality. Trials that did not report on the primary outcome were included.

The interventions in the included trials were allogenic stem cell transplantation, autologous stem cell transplantation and conventional chemotherapy. All but one of the included trials were genetically randomised trials, although three used a mixture of matched related and unrelated donors. The RCT compared autologous stem cell transplantation with chemotherapy (as did four genetically randomised trials); the remaining trials compared allogenic stem cell transplantation with the other treatments. All trials used myeloablative conditioning based on a total body irradiation/cyclophosphamide regimen.

Mean or median patient age ranged from 24 to 40 years; the percentage of high-risk patients ranged from 20 to 100% (where reported). Definitions of high-risk patients varied between trials.

The authors did not report how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed by two reviewers. If a criterion was not reported, this was considered to be an indicator of bias. The criteria used for RCTs were those recommended by the Cochrane Handbook including sequence generation, allocation concealment, blinding and exclusions from analysis. For genetically randomised trials the criteria recommended by Wheatly and Gray were used, including intention-to-treat analysis, timing of patient’s trial entry, tissue typing method, compliance with assigned intervention, and comparability of potential confounders.

Data extraction
The numbers of events for each outcome were extracted in order to calculate relative risk (RR) and 95% confidence intervals (CI). Authors were contacted for missing data.

Two reviewers independently extracted data; a third reviewer extracted the data in cases of disagreement.

**Methods of synthesis**

Relative risks were pooled using a random-effects model, since heterogeneity was expected for disease risk characteristics. Between trial heterogeneity was determined using the $I^2$ statistic, $T^2$ and $\chi^2$ tests.

Analyses were performed for all trials, and separately for intention-to-treat and non intention-to-treat trials. Subgroup analyses were performed for trials of standard-risk patients and high-risk patients. The number-needed-to-treat (NNT) was calculated. Potential confounders were evaluated using the Student $t$ test or as reported in the original trial.

**Results of the review**

Thirteen trials were identified for the review, including 3,562 patients (from table 2, cited as 2,648 in text) with trial sizes ranged from 45 to 1,487 patients. There were 12 genetically randomised trials and one standard RCT (n=117 patients). Trials were not blinded. Some genetically randomised trials did not use an intention-to-treat analysis or evaluate possible confounders between the two arms. Compliance rates ranged from 56 to 95%. The mean duration of follow-up was 62 months, ranging from 30 to 120 months (from table 2, cited as 110 months in text).

**Allogenic stem cell transplantation versus autologous stem cell transplantation or chemotherapy**

There was significantly lower all-cause mortality for allogenic stem cell transplantation versus autologous stem cell transplantation or chemotherapy (RR 0.88, 95% CI 0.80 to 0.97;10 trials with 11 comparisons; $I^2$=27%). Subgroup analysis found a significantly lower all-cause mortality for standard-risk patients for allogenic stem cell transplantation versus the other treatments (RR 0.80, 95% CI 0.68 to 0.94; three trials; $I^2$=0%); the reduction in all-cause mortality was not significant for high-risk patients (eight trials), but had moderate heterogeneity ($I^2$=55%). Subgroup analyses found the reduction in all-cause mortality was significant for trials with an intention-to-treat analysis (RR 0.89, 95% CI 0.82 to 0.97; seven trials; $I^2$=0%; NNT=17, 95% CI 9 to 50), but not for trials without an intention-to-treat analysis (four trials with moderate heterogeneity, $I^2$=60%). Subgroup analysis for standard-risk patients and intention-to-treat trials also found a significantly lower all-cause mortality for allogenic stem cell transplantation versus other treatments (two trials; no heterogeneity; NNT=11, 95% CI 6 to 100). The results for subgroup analyses comparing intention-to-treat and non intention-to-treat trials of high-risk patients were not significant.

**Autologous stem cell transplantation versus chemotherapy**

There was no significant difference in all-cause mortality for autologous stem cell transplantation versus chemotherapy (five trials; $I^2$=46%). Subgroup analyses found no significant differences for standard-risk patients (two trials; $I^2$=64%) or high-risk patients (four trials). There was a significant increase in non-relapse mortality for autologous stem cell transplantation versus chemotherapy (RR 1.77, 95% CI 1.12 to 2.80; two trials), but no significant difference in recurrence rate (three trials, $I^2$=74%).

Analyses omitting the largest trial showed that this trial appeared to have a significant effect on the overall results.

**Authors’ conclusions**

Allogenic stem cell transplantation was a superior treatment compared with autologous stem cell transplantation or chemotherapy for patients with acute lymphoblastic leukaemia in first complete remission. The survival advantage was of greater statistical significance for patients with standard-risk acute lymphoblastic leukaemia than for patients with high-risk acute lymphoblastic leukaemia.

**CRD commentary**

The review addressed a well-defined question for participants, interventions and relevant outcomes, but the details of relevant study design were not very clear for genetically randomised trials. Relevant databases were searched in any language; unpublished studies were considered. Publication bias was not assessed. Efforts were made to minimise error...
and bias in data extraction and validity assessment, but it was not reported whether such measures were applied to study selection.

Trial quality was assessed using suitable criteria and two methods, but few details were reported, which made it more difficult to assess trial quality. The total number of patients given in the tables did not match with the total given in the text. Relevant trial details were reported, but no chemotherapy details were provided. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis of the trials seemed appropriate. The evidence was mostly derived from genetically randomised trials of uncertain quality.

In view of some potential limitations arising from the review process, and limitations to the evidence presented including a small number of trials with small sample sizes, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice**: The authors did not state additional implications for practice.

**Research**: The authors identified a need for intention-to-treat-based genetically randomised trials of high-risk patients which assess different high-risk features to evaluate the best post-remission treatment. They suggested that future trials should assess the role of tyrosine kinase inhibitors, reduced intensity conditioning, and alternative donor allogenic stem cell transplantation. Future trials should also aim to report all-cause mortality, apply uniform risk criteria when reporting the outcomes of different subgroups, and attempt to minimise the risk of bias. Comparisons between autologous stem cell transplantation and chemotherapy should be made in future trials.

**Funding**

Not stated.

**Bibliographic details**


PubMedID

20564092

DOI

10.1002/cncr.25136

Original Paper URL


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adult; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Humans; Precursor Cell Lymphoblastic Leukemia-Lymphoma /drug therapy /mortality /therapy; Randomized Controlled Trials as Topic; Recurrence; Remission Induction

**AccessionNumber**

12010005941

**Date bibliographic record published**

03/11/2010
Date abstract record published
11/05/2011

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.