Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: systematic review and meta-analysis

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CRD summary
According to available evidence, paediatric-inspired regimens were superior to conventional adult chemotherapy in adolescents and young adults with acute lymphoblastic leukaemia. The authors' conclusions reflect the evidence presented but one should mind the methodological limitation of the evidence (no randomised controlled trials) and the issue of generalisability to those aged over 20 years when interpreting the results.

Authors' objectives
To evaluate the efficacy and safety of paediatric-inspired regimens given to adolescents and young adults (defined as 16 to 39 years) with acute lymphoblastic leukaemia.

Searching
MEDLINE was searched from 1971 to May 2011 and relevant conference proceedings papers (American Society of Haematology, American Society of Clinical Oncology and European Haematology Association) were searched from 2004 to 2010. There were no language restrictions. Search terms were reported. Relevant reference lists from all identified articles were handsearched.

Study selection
Studies that allocated adolescents and young adults patients with acute lymphoblastic leukaemia to either paediatric-inspired or a conventional adult regimen of chemotherapy were eligible for inclusion. Studies such as randomised controlled trials, cohort studies, case-control and nested case-control studies which a priori (before starting induction chemotherapy) allocated patients to either paediatric-inspired or a conventional adult regimen were eligible for inclusion.

The primary outcome was all-cause mortality at three years and at the longest available follow-up. Secondary outcomes included post-induction complete remission rate, event-free survival, relapse rate and non-relapse mortality.

Median age of the patients who received paediatric-inspired regime ranged from 12.9 to 31 years and conventional-adult regime ranged from 16.9 to 29 years. The percentage of patients who received haematopoietic cell transplantation (HCT) varied across the trials. In most studies, paediatric-inspired regimes used higher median doses of corticosteroids, vincristine, asparaginase and intrathecal methotrexate but lower median doses of daunorubicin, cytarabine and etoposide.

Two reviewers screened the title and abstracts of the identified studies. In case of disagreement, a third reviewer independently inspected the full article.

Assessment of study quality
Cohort and case-control studies were assessed using the Newcastle-Ottawa scale. The assessment included three major parameters: selection of cohort and controls, comparability of the selected cases and controls based on age and disease, and adequacy assessment of outcomes (defined as at least three years from treatment allocation).

The authors did not state how many reviewers were involved in quality assessment.

Data extraction
Data were extracted to calculate relative risk (RR) for dichotomous outcomes with corresponding 95% confidence intervals (CIs).

The authors did not state how many reviewers were involved in data extraction.

Methods of synthesis
Data were combined using a fixed-effect model to calculate overall relative risks (RR) with their corresponding 95% confidence intervals. $\chi^2$ and $I^2$ were used to assess heterogeneity between studies. $I^2$ of 50% was considered sufficiently heterogeneous to indicate use of a random-effects model.

A funnel plot was inspected to assess publication bias. A subgroup analysis was planned for studies that included younger and older patients (below and above 20 years old). Sensitivity analyses were planned for studies with a quality score higher than 3 and for studies with well-controlled groups (controlled for either age or disease risk). All data were analysed according to the intention-to-treat method.

**Results of the review**

Eleven studies (2,489 patients, range 40 to 926) were included in the review. None of the studies was a randomised controlled trial. Duration of follow-up ranged from 35 to 89 months, where reported. Two studies were rated quality score 2, five studies were rated 3, two studies were rated 5, one rated 6 and one rated 7.

Adolescents and young adult patients given paediatric-inspired regimens had a statistically significant reduction in all-cause mortality at the end of the study period (RR 0.59, 95% CI 0.52 to 0.66; 10 studies; $I^2=24\%$) and at three years (RR 0.58, 95% CI 0.51 to 0.67; eight studies) compared with patients given the conventional adult regimes. The absolute risk reduction for all-cause mortality at three years was 0.20 and the number needed to treat to prevent one death with paediatric-inspired regimens was 5 (95% CI 4 to 7).

Subgroup analysis could not be performed for the patients older than 20 years as the available studies did not report outcomes separately for patients older than 20 years of age. Sensitivity analyses for higher methodological quality and well-controlled studies showed similar results.

Complete remission rate after induction chemotherapy was superior in the paediatric-inspired regimens arm (RR 1.05, 95% CI 1.01 to 1.10; seven studies; $I^2=55\%$) at three years. Patients in the paediatric-inspired regimens had higher event-free survival rates compared with the conventional adult regimes (RR 1.66, 95% CI 1.39 to 1.99; nine studies; $I^2=61\%$). Sensitivity analysis of well-controlled studies for complete remission rate and event free-survival also showed similar results.

There was a statistically significant reduction in relapse rate in the paediatric-inspired regimens compared with the conventional-adult regimes (RR 0.51, 95% CI 0.39 to 0.66; eight studies; $I^2=54\%$). No statistically significant difference was found in the rate of non-relapse mortality between the two groups (RR 0.53, 95% CI 0.19 to 1.48; four studies; $I^2=56\%$).

**Authors’ conclusions**

According to the available evidence, paediatric-inspired regimens were superior to conventional adult chemotherapy in adolescents and young adults with acute lymphoblastic leukaemia. Further randomised controlled studies were needed.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. No language restrictions were applied to the search, which minimised the risk of language bias. Appropriate methods to reduce reviewer error and bias were used for some stages of the study selection process but it was unclear whether similar methods were used for quality assessment and data extraction. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The authors’ conclusions reflect the evidence presented. One should mind the methodological limitations of the evidence (no randomised controlled trials) and the issue of generalisability of the results to the older population (age over 20 years) when interpreting those results, which the authors acknowledged.

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

**Practice:** None.

**Research:** Further randomised controlled trials were needed to investigate paediatric-like approaches versus adult protocols for adolescents and young adults and older adult patients with acute lymphoblastic leukaemia. It was crucial to set the age limit for the feasibility of these protocols.
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