Meta-analysis: Intensive chemotherapy improves survival in childhood acute lymphoblastic leukaemia

Childhood ALL Collaborative Group. **Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. Lancet. 1996 Jun 29;347:1783-8.**

Objective

To determine the association between the duration and intensity of long-term maintenance therapy and mortality and recurrence in children with acute lymphoblastic leukaemia (ALL).

Data sources

Trials were identified using MEDLINE, clinical trials databases, hand searches of meeting abstracts, bibliographies of trials and review articles, and correspondence with colleagues and pharmaceutical companies.

Study selection

Randomised controlled trials were included if they assessed any aspect of primary treatment of ALL and if they began before 1987.

Data extraction

Individual data were collected on sex; leukocyte counts at diagnosis; dates of birth, diagnosis, randomisation, complete remission, relapse, death, or last contact; and treatments.

Main results

42 trials were included. Total events (death or relapse) were reduced with longer maintenance therapy (27.6% vs 23.3%, $P < 0.001$), the addition of vincristine and prednisone pulses (31.2% vs 40.4%, $P < 0.001$), and intensive reinduction (27.8% vs 35.8%, $P < 0.001$). Longer chemotherapy maintenance was associated with a decreased rate of all failures ($P = 0.003$), less relapse in bone marrow ($P < 0.001$), less relapse in testes ($P = 0.009$), and more deaths in the first remission ($P = 0.004$), but not in overall survival. The addition of vincristine and prednisone pulses during maintenance was associated with a decrease in all failures ($P < 0.001$), relapse in bone marrow ($P < 0.001$), and relapse in testes ($P < 0.001$), but not in any death, death in first remission, or death after relapse. Addition of intensive reinduction during maintenance was associated with a decrease in any failure ($P < 0.001$), relapse in bone marrow ($P < 0.001$), relapse in central nervous system ($P < 0.001$), death after relapse ($P < 0.001$), and any death ($P = 0.01$), but not death without remission or death in the first remission. Children who received intensive reinduction during maintenance had an 18.5% death rate compared with a death rate of 22.3% for children who did not receive intensive reinduction. {This 3.8% absolute risk reduction means that 26 children would need to be treated with intensive reinduction (rather than control drugs) to prevent 1 additional death, 95% CI 15 to 129; the relative risk reduction was 16.9%, CI 3.7% to 28.4%.}* Insufficient data were available to evaluate what effects other drug additions during maintenance would have on survival and recurrence.

Conclusions

Total events (death or recurrence) in childhood acute lymphoblastic leukaemia are reduced with longer maintenance therapy, the addition of vincristine and prednisone pulses, and intensive reinduction. Deaths are reduced only with intensive reinduction.

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*Numbers calculated from data in article.

Commentary

Childhood ALL is the most common malignant condition in children. Although survival rates have improved over the past several decades, 1 in 4 children with ALL dies because of the disease or as a consequence of treatment. Hence, clinicians continue to ask how best to optimise the duration and intensity of individual patient therapy without exposing patients to unnecessary toxicity. This systematic review indicates that increasing the duration of maintenance or adding periodic doses of vincristine and prednisone offered little overall benefit to patients: The decrease in relapse rate was offset by an increase in death during remission, resulting in no net change in survival. Conversely, increasing the intensity of reinduction chemotherapy resulted in an improvement in long-term survival that was maintained for more than 5 years of follow-up.

Any interpretation of this analysis of studies that began before 1987 needs to be taken in the context of current therapy because consistent improvement in the results of ALL therapy has occurred. This study provides a solid basis for the current trend towards intensification of induction and consolidation therapy for childhood ALL. This disease is heterogeneous and can be clearly divided into distinct subtypes of prognosis. Current emphasis is on individualising therapy according to low-, intermediate-, and high-risk groups for relapse on the basis of prognostic factors that can be identified at diagnosis. If this approach is used, patients in the higher-risk groups can have an increased rate of survival (1). In addition, the practice of intensifying initial therapy according to risk factors may decrease the benefit of later intensification, as was shown in the studies included in this analysis. New techniques for monitoring minimal residual disease offer another potential tool for individualising therapy.

This article offers good evidence that intensification of therapy improves outcome in this disease and is a strategy worth pursuing. However, more research is required to determine its optimal application.

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Reference

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