CNS-directed therapy for childhood acute lymphoblastic leukemia: childhood ALL
Collaborative Group overview of 43 randomized trials

CRD summary
This review assessed the effect of different therapies directed at the central nervous system in preventing relapses and improving survival in children with acute lymphoblastic leukaemia. This well-conducted review used data from the individual patients and concluded that long-term intrathecal therapy could replace radiotherapy, and that the addition of methotrexate was beneficial. These conclusions are likely to be reliable.

Authors' objectives
To clarify the relative effects on relapse and survival of different therapies directed at the central nervous system (CNS) in childhood acute lymphoblastic leukemia (ALL).

Searching
MEDLINE and EMBASE were searched (dates not given), as were databases (unspecified) of clinical trials. In addition, meeting abstracts, review articles and reference lists were searched, and members of the Childhood ALL Collaborative group and other experts were contacted. Unpublished trials were included in the review.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) in which treatment arms differed only in respect of the CNS-directed therapy used. Trials which began after 1993 were excluded from the review.

Specific interventions included in the review
The inclusion criteria specified cranial or craniospinal irradiation, intrathecal drugs, or intravenous methotrexate or mercaptopurine at a dose of at least 500 mg/m2.

Participants included in the review
The inclusion criteria were unclear, but they appear to be children aged under 21 years at randomisation with a diagnosis of ALL.

Outcomes assessed in the review
The inclusion criteria stated that the main outcomes were event-free survival, where an event is defined as relapse or death, and survival from the date of randomisation. The secondary outcomes assessed were CNS relapses, non-CNS relapses, death in remission, and isolated CNS relapse.

How were decisions on the relevance of primary studies made?
Contact with trial investigators was used to establish the relevance of the primary studies.

Assessment of study quality
The data were checked for internal inconsistencies, imbalances between treatment groups with respect to baseline characteristics, randomisation dates and length of follow-up. Inconsistencies between publications were also checked. Data were checked for evidence of the exclusion of randomised patients or the inclusion of non-randomised patients. Any inconsistencies were clarified and rectified through correspondence with trialists, who then verified summary tables. The authors did not state how decisions on trial validity were arrived at.
Data extraction
Trial investigators were asked to provide data on diagnosis, white cell count at random assignment to treatment, treatment allocation, site of first relapse, first remission, relapse, and death or last contact.

Methods of synthesis
How were the studies combined?
The studies were combined using meta-analyses of IPD. Observed minus expected numbers of events and their variance were calculated for each treatment group in each trial by log rank survival analyses, which used the exact dates of events. These were summed to give totals that were then used to calculate the odds ratios for annual events, along with confidence intervals (CIs) and descriptive survival curves.

How were differences between studies investigated?
Chi-squared tests of heterogeneity and trend were used to assess differences in treatment effect between trials and between different subgroups of patients, based on gender, white cell count and immunophenotype.

Results of the review
Forty-four trials with 8,827 patients were included in the review. A further 17 trials were identified but were not included in the review. IPD could not be obtained from 16 of these, while data from one trial were not requested.

Eight trials examined initial intrathecal therapy followed by cranial irradiation compared with further intrathecal therapy. Data from 7 trials of 2,848 patients were available; the remaining trial for which data were unobtainable involved 350 children. There were no significant differences between the groups in the overall event rate, the annual event rate, overall survival at 10 years, or event-free survival. There were fewer isolated CNS relapses in the cranial irradiation group (4.9%) than in the intrathecal therapy (7.1%) (P=0.03).

Eight trials compared the addition of intravenous methotrexate to long-term intrathecal therapy (up to 12 doses) or radiotherapy with intrathecal therapy (up to 9 doses). Data from all trials, which involved 3,189 patients, were available. There was a significant reduction of 17% (95% CI: 6, 27, P=0.003) in the annual event rate with intravenous methotrexate. Event-free survival at 10 years was higher in the group given intravenous methotrexate (68.1% versus 61.9%). The overall survival rates at 10 years did not differ significantly. The annual rates of non-CNS relapses were 17% lower in the methotrexate group (P=0.02), while the CNS and isolated CNS rates were both non significantly lower in this group.

Three trials (958 patients), which were all available, compared cranial irradiation plus short-term intrathecal therapy with intravenous methotrexate plus short-term intrathecal therapy. Neither 10-year survival nor event-free survival was significantly different between the groups. The CNS relapse rates were 62% lower in the cranial irradiation group (P<0.00001) but the non-CNS relapse rates were 67% higher (P=0.00005).

Seven trials compared different doses of radiotherapy (24 Gy versus 18 or 21 Gy) combined with short-term intrathecal therapy. Six trials involving 809 patients were available. The trial which was unavailable included fewer than 200 patients. There were no significant differences between the doses on any measure.

Three trials (512 patients), all of which were available, compared radiotherapy combined with short-term intrathecal therapy with intravenous methotrexate combined with long-term intrathecal therapy. There were no significant differences between the groups on any measure.

Three trials (511 patients), all of which were available, examined the addition of intravenous methotrexate and intrathecal therapy to other CNS therapies such as cranial irradiation, which was used in all groups in all trials. There were no significant differences between the groups on any measure.

There was no evidence of significant heterogeneity in any of the main comparisons, either between trials or between patient subgroups, based on gender, white cell count or immunophenotype.

Twenty-nine trials addressed comparisons other than those reported above. Data from 14 of these trials were available.
Authors' conclusions
Radiotherapy can be replaced by long-term intrathecal therapy. Intravenous methotrexate gives additional benefit as it reduces non-CNS relapses.

CRD commentary
Some of the inclusion criteria were not explicitly stated, but the objective of the review was clear. The search was reasonably thorough, and publication bias is unlikely as unpublished trials were included in the review. Communication with trialists was appropriate to ensure the eligibility of each trial and the accuracy of the data. The number of trials included and the number for which data were available were clear, as was the size of those trials for which data were unavailable. It was not explicitly stated how many reviewers made decisions on the inclusion and exclusion of studies in the review, or how the data were checked for accuracy. The meta-analysis of IPD was appropriate. The authors' conclusions are appropriate.

Implications of the review for practice and research
Practice: The authors stated that cranial irradiation can be replaced by long-term intrathecal therapy and that intravenous methotrexate improves event-free survival.

Research: The authors did not state any implications for further research.

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