Efficacy of High-Dose Methotrexate in Childhood Acute Lymphocytic Leukemia: Analysis by Contemporary Risk Classifications

By Minnie Abromowitch, Judith Ochs, Ching-Hon Pui, Diane Fairclough, Sharon B. Murphy, and Gaston K. Rivera

High-dose methotrexate (HDMTX) added to a basic regimen of chemotherapy proved superior to cranial irradiation and sequentially administered drug pairs (RTSC) in prolonging complete remissions in children with "standard-risk" acute lymphocytic leukemia. To extend this result to more contemporary risk groups, we reclassified the patients according to methods of the Pediatric Oncology Group (POG), the Childrens Cancer Study Group (CCG), the Rome workshop, and St Jude Total Therapy Study XI. By life table analysis, 70% to 78% of patients with a favorable prognosis would remain in continuous complete remission (CCR) at 4 years if treated with HDMTX. Uniformly lower CCR rates could be expected with RTSC, especially in St Jude better-risk patients. HDMTX also would show greater efficacy than RTSC in the CCG average-risk and POG poor-risk groups, but the results appear inferior to those being achieved with intensified regimens for high-risk leukemia. Although both therapies would provide adequate CNS prophylaxis in favorable-risk groups, RTSC would offer greater protection in patients classified as being in a worse-risk group by St Jude criteria. We conclude that HDMTX-based therapy, as described in this report, would be most effective in patients with a presenting leukocyte count of <25 x 10^9/L of the white race, aged 2 to 10 years, and having leukemic cell hyperdiploidy without translocations.

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HIGH-DOSE METHOTREXATE with leucovorin rescue (HDMTX) has a clear potential for improving the clinical outcome in childhood acute lymphocytic leukemia (ALL). The ability to escalate MTX dosages without producing dose-limiting toxicity should allow one to overcome drug resistance in a high proportion of cases. An equally effective alternative might be the use of non-cross-resistant drug pairs in patients who have achieved complete remission. Thus, in 1979 we began a randomized prospective study to compare the efficacy of these two methods of treatment intensification in children with "standard-risk" ALL. A secondary aim was to assess repeated courses of HDMTX and intrathecal MTX (ITMTX) v 1,800-cGy cranial irradiation and ITMTX administered as CNS prophylaxis early in remission.

Late in the study, it became apparent that our definition of standard-risk ALL was not consistent with the current knowledge of prognostic factors in this disease and could hamper comparisons with results from other centers. We therefore present our findings according to risk groups established by the Childrens Cancer Study Group (CCG), the Pediatric Oncology Group (POG), the Rome workshop, and newer St Jude criteria that include leukemic cell genetic features. Results of this retrospective analysis should be of interest to investigators planning studies of HDMTX as a component of multiagent chemotherapy for childhood ALL.

PATIENTS AND METHODS

From June 1979 to December 1983, 330 consecutive children with newly diagnosed ALL were enrolled in the study. Their presenting features included (a) an initial leukocyte count <100 x 10^9/L; (b) no mediastinal mass, (c) an absence of blasts in the CSF, and (d) blast cells lacking surface immunoglobulin and receptors for sheep erythrocytes (E-).

Bone marrow cells collected at the time of diagnosis were tested for reactivity to a panel of cytochemical stains and were classified as lymphoblastic, either L1 or L2, according to French-American-British (FAB) criteria. Leukemic narrow cells were also separated on a Ficoll-Hypaque gradient and classified as common, T, or undifferentiated on the basis of their reactions with various probes for lymphoblast surface markers. Flow cytometric determinations of DNA content and complete analysis of G-banded karyotypes were performed as previously described.

Treatment protocol. Details of the treatment protocol have been described elsewhere. All patients received identical remission induction therapy for 4 weeks. Those achieving complete remission (CR) were stratified according to age (<2, 2 to 5, 5 to 10, and 10+ years) and initial leukocyte count (<10, 10 to 25, and 25 to 100 x 10^9/L) and randomized with equal probability to either of two treatment groups: HDMTX or cranial irradiation followed by sequentially administered drug pairs (RTSC). The HDMTX arm consisted of 4 infusions of MTX (1,000 mg/m^2 given over 24 hours once a week for 3 weeks and then once every 6 weeks for up to 75 weeks) and coordinated ITMTX (12 mg/m^3) in addition to conventional maintenance therapy of daily oral mercaptopurine (MP) and weekly MTX. The RTSC arm consisted of 1,800-cGy cranial irradiation ITMTX, and the following drug pairs: 6-mercaptopurine–MTX, cyclophosphamide–doxorubicin, and teniposide–cytarabine. In both arms of the study, treatment was given for 30 months, and drug dosages were adjusted to maintain leukocyte counts in the range of 2 to 4 x 10^9/L. All patients received daily trimethoprim–sulfamethoxazole to prevent Pneumocystis carinii infection.

Clinical diagnostic procedures. Surveillance lumbar puncture and bone marrow aspiration were performed every 3 months while patients were receiving therapy and every 4 to 6 months for 2 years after the completion of therapy. CNS disease was diagnosed when lymphoblasts were present in a Wright-stained cytocentrifuged sample of CSF. To be classified as a complete responder, patients had to have adequate recovery of hematopoiesis without detectable lymphoblasts by day 28. Patients who did not achieve CR by day 28...
Table 1. Prognostic Groups After Reclassification

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk Criteria</th>
<th>Patients (%)</th>
<th>HDMTX (n = 154)</th>
<th>RTSC (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Age (yr)</td>
<td>WBC (× 10⁹/L)</td>
<td>FAB Type</td>
<td>Race</td>
</tr>
<tr>
<td>Low</td>
<td>3-6</td>
<td>&lt;10</td>
<td>L1</td>
<td>—</td>
</tr>
<tr>
<td>Average</td>
<td>All others</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>High</td>
<td>0-21</td>
<td>&gt;50</td>
<td>All others</td>
<td>—</td>
</tr>
<tr>
<td>POG⁴</td>
<td>Good</td>
<td>1-10</td>
<td>&lt;10</td>
<td>—</td>
</tr>
<tr>
<td>Poor</td>
<td>All others</td>
<td>3-5</td>
<td>10-99</td>
<td>—</td>
</tr>
<tr>
<td>Rome workshop⁵</td>
<td>Good</td>
<td>1-9</td>
<td>&lt;50</td>
<td>—</td>
</tr>
<tr>
<td>Poor</td>
<td>1, ≥ 10</td>
<td>≥ 50</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>St Jude Study XI⁶</td>
<td>Better</td>
<td>2-9</td>
<td>&lt;25</td>
<td>White</td>
</tr>
<tr>
<td>Worse</td>
<td>≤ -2, ≥ 10</td>
<td>&lt;25</td>
<td>—</td>
<td>Nonwhite</td>
</tr>
</tbody>
</table>

*DNA index of >1.15, no chromosomal translocations.
†DNA index of ≤1.15, chromosomal translocations.

were considered induction failures and were treated with alternative therapy. Informed consent was obtained from the parents or their patients before treatment, and the treatment protocol was approved by the St Jude clinical trials review committee.

Risk classification. Patients were reassigned to risk groups according to the criteria listed in Table 1.

Statistical analysis. The Kaplan-Meier procedure was used to estimate the proportion of patients in continuous complete remission (CCR) at 4 years. Distributions of remission lengths were compared by the log rank test. The estimated SE for the proportions of patients remaining disease free 4 years after the date of high-dose methotrexate (HDMTX) were computed by the method of Peto et al. The median length of follow-up was 5 years (range, 2.5 to 7 years); the findings reported here are based on an update performed in September 1986.

RESULTS

A total of 330 patients were registered in the study, four of whom were declared ineligible during the induction phase of therapy (wrong diagnosis or refusal of treatment). Of the 326 eligible subjects, 309 (95%) entered CR within 4 weeks and were randomized, 154 to the HDMTX-treated group and 155 to the RTSC-treated group. By log rank analysis, patients treated with HDMTX have achieved significantly longer periods of CR than have patients in the RTSC-treated group (P = .049); however, durations of CNS remission are similar (P = .17). Approximately 67% (5% SE) of the HDMTX-treated patients and 56% (5% SE) of those receiving RTSC are expected to be in CCR at 4 years from the date of remission.

The major aim of this analysis was to determine how the superiority of HDMTX in our standard-risk patients applies to more widely accepted risk groups. Table 2 shows 4-year estimates of complete and CNS remission rates according to four different systems of risk classification. Approximately 75% of the favorable-risk patients, regardless of method of selection, could be expected to achieve long-term CR with the HDMTX regimen. There is a clear trend toward superiority of HDMTX over RTSC, with statistical significance achieved in better-risk patients identified by St Jude Study XI criteria (P = .03), in CCG average-risk, and POG poor-risk groups (P = .02). CNS remission rates would be high (>90%) in all favorable-risk groups, regardless of the treatment used. Importantly, RTSC would afford significantly better protection against CNS relapse in patients with St Jude worse-risk features (P = .01).

DISCUSSION

In this randomized clinical trial, HDMTX significantly prolonged CRs in children with standard-risk ALL. Analysis

Table 2. Comparison of 4-Year Remission Rates

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Risk Group</th>
<th>Treatment</th>
<th>HDMTX</th>
<th>RTSC</th>
<th>Risk Group</th>
<th>Treatment</th>
<th>HDMTX</th>
<th>RTSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous complete remission</td>
<td>St Jude XI</td>
<td>Better</td>
<td>.78 (.06)</td>
<td>.62 (.06)</td>
<td>Worse</td>
<td>.49 (.07)</td>
<td>.47 (.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CCG</td>
<td>Low</td>
<td>.73 (.09)</td>
<td>.62 (.09)</td>
<td>Average</td>
<td>.65 (.06)</td>
<td>.52 (.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>POG</td>
<td>Good</td>
<td>.72 (.06)</td>
<td>.63 (.06)</td>
<td>Poor</td>
<td>.61 (.07)</td>
<td>.45 (.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rome workshop</td>
<td>Good</td>
<td>.70 (.06)</td>
<td>.58 (.06)</td>
<td>Poor</td>
<td>.60 (.06)</td>
<td>.48 (.09)</td>
<td></td>
</tr>
<tr>
<td>Continuous CNS remission</td>
<td>St Jude XI</td>
<td>Better</td>
<td>.97 (.02)</td>
<td>.94 (.04)</td>
<td>Worse</td>
<td>.74 (.08)</td>
<td>.95 (.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CCG</td>
<td>Low</td>
<td>.92 (.04)</td>
<td>.94 (.03)</td>
<td>Average</td>
<td>.87 (.04)</td>
<td>.94 (.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>POG</td>
<td>Good</td>
<td>.92 (.03)</td>
<td>.93 (.04)</td>
<td>Poor</td>
<td>.84 (.06)</td>
<td>.97 (.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rome workshop</td>
<td>Good</td>
<td>.92 (.03)</td>
<td>.95 (.06)</td>
<td>Poor</td>
<td>.78 (.08)</td>
<td>.91 (.06)</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated SE are in parentheses.
of the results according to several different methods of risk assignment confirmed the efficacy of HDMTX in patients with more favorable presenting features; all others would likely derive greater benefit from one of the intensified regimens being used to treat high-risk ALL. Because the combination of ITMTX and HDMTX provided adequate CNS prophylaxis in all favorable-risk groups, we conclude that it can be substituted for cranial irradiation in such patients. However, there was a clear advantage from the use of 1,800-cGy cranial irradiation as CNS prophylaxis in patients with less favorable prognostic features. The efficacy of this lower radiation dose supports data of Nesbit et al showing that 1,800 cGy is as effective as 2,400 cGy.

The concept of improving basic regimens of chemotherapy by increasing the MTX dosage is well established in leukemia research, but the optimal dose escalation remains controversial. Freeman et al have reported results for patients with a standard risk of failure who received three courses of IVMTX at 500 mg/m^2 early in the consolidation phase of therapy. Although improved protection against hematologic relapse was demonstrated, the rate of CNS relapse remained high. Hence, the overall outcome (4-year CCR rate of 58%) showed no improvement over that for patients receiving cranial irradiation and conventional MP and MTX maintenance therapy. Green et al compared the efficacy of three courses of IVMTX at 500 mg/m^2 vs six courses at 500 and 1,500 mg/m^2 for patients with leukocyte counts >30 x 10^9/L and found that the latter regimen increased CR durations but did not decrease the incidence of primary CNS relapse. Moe et al, using three courses of MTX at 500 mg/m^2, obtained an actuarial long-term disease-free survival rate of 68% in standard-risk patients and one of 44% in patients with an increased risk of relapse. The CNS relapse rate in their study was 10%, similar to ours. Pollow et al escalated the MTX dosage to more than 33,000 mg/m^2 in an attempt to improve control of CNS relapse. Although this intensive regimen was adequately tolerated, it has not shown greater efficacy than previous treatments incorporating lower amounts of MTX.

Recent findings in a subset of our patients indicate that variability in drug elimination resulted in a wide range of steady-state serum MTX concentrations and that subjects with concentrations of less than 16 μmol/L in the serum were twice as likely to have a relapse as those with higher concentrations. A loading dose of 200 mg/m^2 and a 24-hour infusion of 1,200 mg/m^2 were recommended for future protocols to avoid HDMTX therapy that would likely be ineffective.

We have demonstrated that the addition of HDMTX to a conventional antileukemic regimen will produce results in favorable-risk patients that are equivalent to those of recently reported therapeutic programs. For all other patients, HDMTX as the sole protocol modification would appear inferior to more intensive multitagent regimens but may be an important component of such therapy. Patients with presenting leukocyte counts <25 x 10^9/L, of the white race, aged 2 to 10 years, and having a hyperdiploid karyotype lacking translocations should derive the greatest benefit from this treatment.

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REFERENCES

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