Comparison of Central Nervous System Prophylaxis With Cranial Radiation and Intrathecal Methotrexate Versus Intrathecal Methotrexate Alone in Acute Lymphoblastic Leukemia

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In acute lymphoblastic leukemia (ALL), central nervous system (CNS) prophylaxis with cranial irradiation plus 5 doses of intrathecal methotrexate (i.t. MTX) reduces the incidence of CNS relapse to 7%-15%. However, increased evidence of CNS delayed toxicity started to be recognized as CT scan abnormalities and neuropsychologic alterations, mainly in children. Two questions were analyzed in the present report: (1) Will further doses of i.t. methotrexate and dexamethasone (i.t. MTX-DMT) decrease the incidence of CNS relapse in patients treated early in remission with cranial irradiation plus i.t. MTX-DMT even more? (2) Is i.t. MTX-DMT given during induction and maintenance equally as effective as cranial irradiation plus i.t. MTX-DMT? A randomized study was designed to answer the first question. Incidence of primary CNS relapse in i.t. MTX-DMT-treated patients with a WBC count less than 50,000 was 11% (15 of 135 patients) and was 11% (17 of 150) in the untreated group. In patients with a WBC count >50,000, it was 16% (6/37) in the treated group and 19% (6/31) in the control group. No difference was observed according to treatment in both prognostic groups. Patients in this study were retrospectively compared with a consecutive protocol in which patients received 3 doses of i.t. MTX-DMT alone during induction plus 3 doses weekly during the first month of remission and every 3 mo thereafter. The incidence of primary CNS leukemia at 60 mo in patients with a WBC count less than 50,000 was 20% in the irradiated group and 32% in the group with i.t. MTX-DMT alone. This difference was not significant. However, the relapse-free survival at 60 mo was 26% and 41%, respectively, (p < 0.0005). The incidence of primary CNS relapse in patients with a WBC count more than 50,000 at 48 mo was 28% in the irradiated group and 42% in the nonirradiated group. The difference was not significant. The duration of complete remission was similar, remaining at 15% and 16% of patients disease-free at 48 mo, respectively. We conclude that (A) after cranial irradiation plus i.t. MTX-DMT X 5, the use of additional doses of i.t. MTX-DMT is not of further benefit in preventing CNS relapse; (B) the use of i.t. MTX-DMT alone compares similarly with cranial irradiation plus i.t. MTX-DMT in the incidence of CNS relapse; and (C) relapse-free survival and survival in patients with a WBC count less than 50,000 were significantly longer in those without cranial irradiation.

CENTRAL NERVOUS SYSTEM (CNS) prophylaxis with cranial irradiation plus intrathecal (i.t.) methotrexate (MTX) or craniospinal irradiation decreased the incidence of primary CNS leukemia from 50%-70% to 5%-12%. Craniospinal irradiation has been reported to produce moderate to marked myelosuppression, prolonged depletion of the T-lymphocyte subpopulation, and potential growth retardation. However, more recently, the long-term deleterious effects have started to be recognized, mainly intracranial abnormalities demonstrable with computed tomography (CT) of the head and neuropsychologic alterations.

Intrathecal MTX alone, given in a short period (5-6 doses) after complete remission is achieved, reduces the incidence of CNS leukemia to 18%-40%; however, the incidence was higher than that obtained by cranial irradiation plus i.t. MTX.

These studies were undertaken to answer two main questions in relation to CNS prevention in patients with acute lymphoblastic leukemia (ALL): (1) After CNS prophylaxis with radiotherapy to the cranial and simultaneous administration of i.t. MTX and dexamethasone (DMT), can the incidence of CNS relapse be further reduced with additional doses of i.t. MTX-DMT during maintenance therapy? (2) How does the so-called "standard" CNS preventive regimen (cranial irradiation plus i.t. MTX) compare with a regimen that includes repeated doses of i.t. MTX-DMT during induction and maintenance?

MATERIALS AND METHODS

Two consecutive GATLA protocols for previously untreated ALL were evaluated in April 1982. Protocol 10-ALL-72 was started in October 1972 and closed in December 1975. A total of 353 patients (310 children and 43 adults) were evaluable. Induction therapy
consisted of 4 weekly doses of vincristine (1.5 mg/sqm) and daily prednisone (40 mg/sqm). If, by day 28, complete remission was not obtained, daunomycin (30 mg/sqm) was added weekly to the above-mentioned drugs. Half of the patients received, at random, consolidation with one dose of cyclophosphamide (600 mg/sqm) and 5 daily doses of arabinosyl cytosine (100 mg/sqm).

A further randomization was made to evaluate two maintenance treatments: 6-mercaptopurine (100 mg/sqm) daily and MTX (15 mg/sqm) twice weekly versus 6-mercaptopurine (600 mg/sqm) and MTX (30 mg/sqm) weekly. All the patients received pulses every 3 mo of one dose of vincristine (1.5 mg/sqm) and a week of prednisone (40 mg/sqm daily). All patients received 2.5 wk of cranial irradiation (2,400 rad) from supervoltage equipment through opposing lateral ports, including the retro-orbital space, superior edge of the zygoma, and first two cervical segments. The dose was reduced to 1,800 rad for children under 2 yr of age. A radiotherapy committee review was not performed for this study. Also, during the period of induction therapy, patients were given 5 doses twice a week of i.t. MTX (12 mg/sqm), with a maximum of 15 mg, and DMT (4 mg/sqm). All the patients were randomized to receive i.t. MTX-DMT one dose every 3 mo or lumbar puncture every 3 mo for CSF study only for 4 yr. The two other variables in the protocol: consolidation versus nothing and weekly versus daily 6-mercaptopurine, were equally effective in prolonging the duration of complete remission. A total of 172 patients who achieved complete remission and completed cranial irradiation plus 5 doses of i.t. MTX-DMT were randomly allocated to further i.t. treatment every 3 mo, and 181 were followed with CSF studies only. Fourteen patients (4%) with initial CNS leukemia, who achieved complete remission, were excluded from the study.

Protocol 1-ALL-76 was started in January 1976 and closed in December 1978. A total of 349 patients (306 children and 43 adults) were evaluable. Twelve patients (3%) with initial CNS leukemia were excluded. Induction therapy consisted of vincristine (1.5 mg/sqm/weekly) and prednisone (40 mg/sqm/daily) alone in children with a WBC count less than 20,000 and daunomycin (30 mg/sqm/weekly), vincristine (1.5 mg/sqm/weekly), and prednisone (40 mg/sqm/daily oral) in the remaining children and all adults. All the patients received consolidation with one dose of cyclophosphamide (600 mg/sqm/i.v.) and 5 daily doses of arabinosyl cytosine (100 mg/sqm/sec) and maintenance with 6-mercaptopurine (100 mg/sqm) daily and MTX (15 mg/sqm/oral) twice a week. All the patients were randomly allocated to receive vincristine (1.5 mg/sqm/i.v. × 1) and prednisone (40 mg/sqm/daily × 7) every month for 6 mo, and thereafter, every 3 mo, or sequential reinduction with vincristine (1.5 mg/sqm/i.v. × 1), prednisone (40 mg/sqm/daily × 7), arabinosyl cytosine (100 mg/sqm/daily × 5), or cyclophosphamide (600 mg/sqm/i.v. × 1).

All the patients received 3 doses of i.t. MTX (12 mg/sqm) and DMT (4 mg/sqm) during induction days 1, 15, and 28, 3 weekly doses in the first month of complete remission, followed by one dose every 3 mo for 4 yr. Fifty milligrams of methotrexate was diluted in 20 cc of distilled water. Dexamethasone was added in the same syringe. The patient was injected in the seating position and remained lying flat for 15 min. Dexamethasone was employed because, in a previous study, we observed that it reduced the side effects of i.t. MTX. The duration of CNS remission was measured from the time complete remission was achieved to the moment isolated CNS relapse was detected, or simultaneously with bone marrow or testis relapse. All the patients who died in complete remission or had isolated bone marrow or testis relapse were considered as lost to follow-up at that time.

The main difference in maintenance was that, in protocol 1-ALL-72, reinduction was performed every 3 mo, and in protocol 1-ALL-76, every month during the first 6 mo and every 3 mo thereafter.

CNS relapse was documented as the unequivocal presence of lymphoblasts in cerebrospinal fluid (CSF). Cytocentrifuge or cyto-sedimentation methods were used for cytologic study of the cells. Life table methods were employed to obtain the curves, and the log rank test was used to compare the incidence of relapse among the curves. To establish the incidence curve of CNS leukemia, patients who had bone marrow or testis relapse or died in complete remission without CNS relapse were considered as lost to follow-up during this interval. To test the difference between proportions, a chi-square test was used.

![Fig. 1](www.bloodjournal.org) **Incidence of CNS relapse in ALL patients with a WBC less than 50,000 according to maintenance CNS therapy after craniocervical irradiation plus i.t. MTX × 5 (protocol 10-ALL-72).**
RESULTS

Comparison of i.t. MTX-DMT Versus Nothing During Maintenance of Remission

All the 353 patients of protocol 10-ALL-72 who achieved complete remission were randomly allocated to both schedules. Patients were stratified according to WBC count at diagnosis.

The incidence of primary meningeal relapse in patients with a WBC count less than 50,000 initially was 11% (15 of 135) in the treated group and 11% (17 of 150) in the untreated group. The incidence of primary meningeal relapse, by actuarial curve, at 84 mo was 19% and 20%, respectively, without any significant difference between both groups (Fig. 1).

In patients with an initial WBC of more than 50,000, the incidence of primary meningeal relapse was 16% (6 of 37) in the treated group and 19 (6 of 31) in the untreated group. The incidence of primary meningeal relapse, by actuarial curve, at 72 mo was 27% and 26%, respectively (Fig. 2). This difference was not significant. No CNS relapse was observed after 36 mo in patients whose WBC was less than 50,000, nor after 24 mo in patients whose WBC was more than 50,000.

Comparison of CNS Relapse With Cranial Irradiation Plus i.t. MTX-DMT Versus i.t. MTX-DMT Alone During Induction and Maintenance

For the purpose of this study, we compared the 353 patients of protocol 10-ALL-72 who had received cranial irradiation plus at least 5 doses of i.t. MTX-DMT during irradiation with 349 patients treated with protocol 1-ALL-76, who received only i.t. MTX-DMT (3 doses during induction, 3 weekly doses during the

<table>
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<tr>
<th>First Event</th>
<th>n</th>
<th>Percent</th>
<th>Percent at 60 mo</th>
<th>n</th>
<th>Percent</th>
<th>Percent at 60 mo</th>
<th>p</th>
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<td>Bone marrow</td>
<td>198</td>
<td>56</td>
<td>66</td>
<td>110</td>
<td>32</td>
<td>47</td>
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<td>22</td>
<td>67</td>
<td>19</td>
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<td>3</td>
<td>10</td>
<td>13</td>
<td>4</td>
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<td>NS</td>
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<tr>
<td>Lymph node</td>
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<td>7</td>
<td>12</td>
<td>36</td>
<td>10</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Still in CR</td>
<td>74</td>
<td>21</td>
<td>21</td>
<td>123</td>
<td>35</td>
<td>31</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Total no. patients</td>
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<td></td>
<td></td>
<td>349</td>
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first month of maintenance, and every 3 mo thereafter). The incidence of first event (bone marrow, CNS, testis, lymph nodes, or death in complete remission) is shown in Table 1 for all the patients of both groups. Twenty-two percent and 37% of the patients with and without cranial irradiation had experienced first CNS relapse at 60 mo, respectively. This difference at the moment is not significant. At 36 mo, the incidence of CNS was 20% and 23%, respectively. Most of the relapses observed in continuous complete remission after 36 mo were in the group without cranial irradiation. Sixty-six percent and 47% had bone marrow relapse as first event at 60 mo \((p < 0.0005)\). Also, 21% of the patients who received cranial irradiation and 31% of those without cranial irradiation remain in their first complete remission at 60 mo \((p < 0.005)\).

The incidence of primary meningeal relapse in patients with a WBC count less than 50,000 initially and who received cranial radiotherapy plus i.t. MIX-DMT was 11% (32 of 285). However, in patients who received i.t. MTX-DMT alone, the incidence was 17%
(49 of 284). The actuarial curves show no differences, with an incidence of primary CNS leukemia at 60 months of 20% and 32% respectively (Fig. 3). No CNS relapse was observed in the irradiated group after 48 mo and after 60 mo in the nonirradiated group.

If we analyze the group of patients with a WBC more than 50,000, the incidence of CNS relapse in patients with cranial radiation plus i.t. MTX-DMT was 18% (12 of 68) compared with 28% (18 of 65) in the nonirradiated group. The actuarial curve at present does not show statistical difference, with an incidence of 28% and 42%, respectively, at 48 mo (Fig. 4).

If we compare the duration of complete remission to first event (bone marrow, CNS, or testicular relapse and death in complete remission), patients with a WBC count of less than 50,000 at diagnosis who received cranial irradiation have a higher incidence of relapse, with 26% remaining alive without relapse at 60 mo, compared with 41% for those who received i.t. chemotherapy alone. The difference was highly significant \((p < 0.0005)\) (Fig. 5). No relapse or death were observed after 60 mo in the group with cranial irradiation, with 16 patients with more than 96 mo since complete remission was achieved.

There was no difference between regimens in the duration of relapse-free survival in patients with a WBC of more than 50,000, with 15% of the cranial irradiation group alive without relapse at 48 mo, compared with 16% in the i.t. group alone (Fig. 6). Also, no relapse was observed after 60 mo.

Survival

The percent survival at 60 mo in patients with a WBC of less than 50,000 and cranial irradiation was 31%, and 47% in those without cranial irradiation \((p < 0.001)\) (Fig. 7). In patients whose WBC count was more than 50,000, the percent survival was 12% and 23%, respectively, \((p < 0.05)\) (Fig. 8). Age and CNS Relapse

The 312 patients \(\leq 15\) yr old with cranial radiotherapy had an incidence of initial CNS relapse at 36 and 60 mo of 21% and 24%, respectively, while the 307 patients who did not receive radiation therapy had an incidence of 23% and 36%, respectively. In 41 adults who received cranial irradiation, there was an incidence of CNS relapse of 9% and 9%, respectively, at 36 and 60 mo, while the 42 patients without cranial irradiation had 15% and 34% of initial CNS relapse, at 36 and 60 mo, respectively. None of the differences is statistically significant. However, we can observe that, in those with cranial irradiation, the incidence of relapse is higher in children than in adults, and practically no relapse was observed after 36 mo. In patients without cranial irradiation, the incidence of relapse was similar in children and in adults, and the incidence of relapse at 60 mo increased, with 15% relapsing after 36 mo.

Neuropsychologic Toxicity

Neurologic, psychopedagogic, and psychologic long-term sequelae were evaluated in 19 patients who received cranial irradiation plus i.t. MTX-DMT and in 23 patients with i.t. MTX-DMT alone after 3 yr of continuous complete remission. This study was published elsewhere.\(^8\) The most important findings were: 58% of the irradiated group showed abnormal CT scans of the cranium compared to 4% of the nonirra-

![Fig. 5. Duration of remission in ALL to first event (CNS, bone marrow, testis relapse, or death) according to CNS prevention regimen (WBC less than 50,000) (protocols 10-ALL-72 and 1-ALL-76).](image-url)
diated group ($p < 0.0005$). Neuropsychologic evaluation (performed by L. Bender technique and Picq-Vayer scale) showed more severe impairment (grade 3–4) in 42% and 0% of the patients, respectively ($p < 0.001$). A new study performed 30 mo after the first one showed 50% of persistent abnormal CT scans in the irradiated group versus 12% in the nonirradiated group. Only 1 patient with neuropsychologic impairment improved in the group with cranial irradiation, and the others remained with the same difficulties. One patient in the nonirradiated group developed alterations in psychomotor coordination.

**DISCUSSION**

The development of effective methods for CNS prevention in acute lymphoblastic leukemia has been regarded as one of the major advances in the control and cure of this disease in the last decade. Not only have there been reductions in the incidence of CNS leukemia from 50%–70% to 5%–15%, but there have also been increases in relapse-free survival.

Several methods have been employed. Some are less effective, e.g., i.t. MTX given for 5 to 6 doses in early remission, or an intermediate dose of i.v. MTX plus i.t. MTX.

![Graph showing survival in ALL according to CNS prevention regimen with WBC less than 50,000 (protocols 10-ALL-72 and 1-ALL-76).](image1)

**Fig. 7.** Survival in ALL according to CNS prevention regimen with WBC less than 50,000 (protocols 10-ALL-72 and 1-ALL-76).
Nesbit et al.\textsuperscript{28,29} reported that isolated CNS relapse was significantly higher ($p < 0.001$) in a group that received i.t. MTX only for 6 doses, compared to one that received craniospinal radiation or cranial radiation plus i.t. MTX for 6 doses. However, there is no significant difference in the proportion of bone marrow relapse or survival among groups. The authors suggest that improvements in survival are probably the result of more effective systemic chemotherapy and better general management. In patients with an initial WBC count <20,000/cumm, they report an 11% incidence of CNS relapse at 6 yr with cranial radiotherapy plus i.t. MTX and 34% in those with 6 doses of i.t. MTX only; 14% and 72%, respectively, in those with a WBC of more than 20,000. They did not include routine lumbar punctures in the study during maintenance therapy, and this can be the reason for the lower incidence of CNS relapse compared to our study.

Probably the most effective method is craniospinal irradiation, which produces a 0%--7% incidence of CNS relapse.\textsuperscript{2,8} However, it appears to be the most toxic method, producing moderate to marked myelodepression and prolonged depletion of the T-lymphocyte subpopulation, which predisposes to an increased risk of major infections.\textsuperscript{10,11} Spinal irradiation will result in a short sitting height; these direct growth effects will be more apparent when CNS irradiation is given during infancy.

All of the above are reasons why craniospinal irradiation has been discontinued as preventive method in most of the groups.

Cranial irradiation with 2,400 rads plus 5 doses of i.t. MTX given early in remission was first developed by the St. Jude group\textsuperscript{1} and was used worldwide thereafter. In patients with a follow-up exceeding 3 yr, between 6% and 14% developed CNS relapse.\textsuperscript{2,3,6,8}

In the present randomized study, we demonstrated that further injections of i.t. MTX given during maintenance therapy every 3 mo for 4 yr in patients who received cranial irradiation plus 5 doses of i.t. MTX did not significantly decrease the incidence of primary CNS leukemia.\textsuperscript{13,24}

More recently, some studies demonstrated that cranial irradiation may produce long-term deleterious toxicity to the CNS. Peylan-Ramu et al.\textsuperscript{19} report that 17 of 32 patients (53%) who received cranial irradiation plus i.t. MTX had one or more abnormal CAT scan findings, while only one CT scan was clearly abnormal from 43 patients treated with i.t. MTX alone or i.t. MTX combined with intermediate dose i.v. MTX without cranial irradiation.\textsuperscript{30}

In contrast to the high number of CT abnormalities in the above-mentioned study, Day et al.\textsuperscript{31} found only 1 abnormal CT scan among 28 children who had received prophylactic cranial radiation and i.t. MTX.

Neuropsychologic studies performed in patients of both groups of the present study also show a higher percent of abnormal CT scans and psychomotor coordination in those who received cranial irradiation. This alteration remained stable in a further study performed approximately 30 mo after the first one.\textsuperscript{18}

The difference in variance results among these studies is difficult to explain. In our study, the i.t. chemotherapy was performed during induction and...
maintenance, while the group reported by Day31 used it only during induction. From January 1976 to December 1978, all the acute lymphoblastic leukemia patients were treated with a protocol of i.t. MTX-DMT given alone during induction and periodically for the following 4 yr of maintenance. The incidence of primary CNS leukemia was compared with a similar number of treated patients, entered from October 1972 to December 1975, in a protocol that included cranium irradiation plus i.t. MTX. The incidence of CNS relapse measured by actuarial curves in patients with a WBC of less than 50,000 was higher in the group without cranial irradiation, mainly due to CNS relapse after 36 mo; however, this difference was not significant. Relapse-free survival was statistically significantly longer (p < 0.0005) in patients treated with i.t. MTX alone, with 41% of patients remaining alive without any relapse at 60 mo compared to 26% in the group with cranial irradiation plus i.t. MTX. This was mainly due to higher incidence of bone marrow relapse in the irradiated group.

Freeman et al.22 have also reported recently that, in standard risk (ages between 2 and 7 and WBC less than 30,000), the incidence of CNS relapse was lower in patients treated with cranial irradiation plus i.t. MTX (11/120) compared to intermediate dose of i.v. MTX in 3 courses plus i.t. MTX (23/117) (p = 0.02). However, the systemic relapse was statistically superior (24/120) in the irradiated group compared with i.t. MTX alone (9/117) (p < 0.01). Both groups of patients received 6 doses of i.t. MTX alone without maintenance.

A retrospective comparison was also made recently of three methods of CNS prophylaxis employed in three different institutions: (1) i.t. MTX alone ×5 doses, (2) intermediate dose MTX infusion and i.t. MTX, and (3) cranial irradiation and i.t. MTX.12 In spite of the fact that meningeal relapse was significantly less frequent among standard risk patients entered with cranial irradiation than among intermediate dose MTX (p = 0.042) or only i.t. MTX ×5 doses (p = 0.001), disease-free survival on intermediate dose MTX was significantly better than that in patients treated with i.t. MTX alone (p = 0.003) or cranial irradiation plus i.t. MTX. The lack of validity of this retrospective study must be emphasized, because the various groups of patients had received widely different systemic chemotherapy, were treated at different time periods, and were followed differently.

The incidence of CNS relapse in high risk patients (WBC >50,000) in our study was higher in the group treated with i.t. MTX alone; however, this difference was not significant either, and the relapse-free survival of both groups was similar.

Sullivan et al.14 report the experience of the Pediatric Oncology Group (POG) comparing triple i.t. MTX therapy, hydrocortisone, and cytosine arabinoside bimonthly with cranium radiotherapy with 5 doses of i.t. MTX. There were no differences between methods in CNS remission duration: 4 of 100 patients versus 6 of 99 patients, respectively, developed CNS leukemia. Duration of bone marrow remission was significantly better in poor prognostic patients treated with i.t. chemotherapy alone, medians 159+ wk versus 43+ wk in patients treated with cranial irradiation (p < 0.05). Systemic chemotherapy was considerably different for the irradiated group than for the triple i.t. chemotherapy group. This difference might influence the results.

In another earlier study designed by the POG12 in 1971, in which children with acute lymphoblastic leukemia were randomized to one of two treatment options for CNS prophylaxis, all patients received i.t. therapy over a 1-yr period with MTX, hydrocortisone, and arabinosyl cytosine. Half of the patients also received 2,400 rad of cranial radiation. There was no significant difference in CNS relapse, length of hematologic remission, or survival between the two groups. Twenty-four percent of the whole group remains in hematologic remission and 30% survive. Patients who remain alive have been followed for a minimum of 8 yr after diagnosis.

Recently, Bleyer et al.33 have reported that i.t. MTX given at the same frequency but with a dose regimen derived from CNS volume considerations (rather than based on body surface area, as employed in our study) was associated with a reduction in CNS relapse rate that was statistically significant. The cumulative 3-yr CNS relapse rate declined from 8%-12% to 5%-7% (p < 0.003). In high risk patients, the decline was from 19%-27% to 6% (p < 0.0001).

However, it has become clear that, despite a tremendous advance in CNS prevention regimens made during the last 10 yr, it is still difficult to recommend a common regimen for all patients; perhaps the methods of CNS prevention should be adapted to the prognostic group and the other phases of treatment.

We can conclude that: (1) after 2,400 rad of cranial irradiation and 5 doses of i.t. MTX-DMT, administration of further doses of i.t. MTX-DMT every 3 mo does not add any benefit in preventing CNS disease. (2) In patients with a WBC less than 50,000, the use of early doses of i.t. MTX-DMT followed by one trimesterly dose offers a slightly lower effectiveness than cranial irradiation plus i.t. MTX-DMT in the prevention of
CNS relapse, mainly due to late CNS relapse (after 36 mo). However, systemic relapse was significantly lower in the group without cranial irradiation. The duration of disease-free survival and survival was also statistically higher in the group without cranial irradiation. (3) In the high risk group (WBC >50,000), CNS leukemia incidence was higher in the group without cranial irradiation. However, the incidence of systemic relapse was lower and the duration of relapse-free survival and survival was the same in both groups.

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REFERENCES


APPENDIX

This study was conducted in the following institutes by these investigators:


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(8) Hospital de Niños (Córdoba): F. Ojeda.


(15) Policlinico Mariano Castex (Buenos Aires): M. Palau y S. C. de Sica.

(16) CEMIC (Buenos Aires): A. Suarez.

(17) Hospital Militar Central (Buenos Aires): A. Musso, M. I. Santos.
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