Efficacy and Morbidity of Central Nervous System “Prophylaxis” in Childhood Acute Lymphoblastic Leukemia: Eight Years’ Experience With Cranial Irradiation and Intrathecal Methotrexate

By Adlette Inati, Stephen E. Sallan, J. Robert Cassady, Suzanne Hitchcock-Bryan, Luis A. Clavell, James A. Belli, and Natalie Sollee

Between 1972 and 1979, 214 children with acute lymphoblastic leukemia and no evidence of central nervous system (CNS) disease prior to CNS prophylaxis were treated with 2400 rad cranial irradiation and concurrent intrathecal methotrexate. Only nine children developed CNS leukemia: five of them in the CNS only and four concurrently in the CNS and another site. Major acute effects of CNS prophylaxis were seizures in seven patients (3%). Sixty-nine children who had a minimum follow-up of 4 yr were evaluable for late effects of therapy. Small cataracts, incomplete regrowth of hair, and learning disabilities were noted. The latter occurred in 18% of patients, an incidence similar to that encountered in a normal community of school-age children. However, the incidence of learning disabilities in patients who were under 5 yr of age at the time of diagnosis was much higher, 35%. We conclude that the combination of cranial irradiation and intrathecal methotrexate was highly efficacious. The incidence and severity of neuropsychologic abnormalities, the principal late morbidity of this treatment program, varies among reporting institutions. Prospective longitudinal studies of neuropsychologic function are necessary to better define the incidence of abnormalities. Future programs should attempt to decrease late morbidity, but must also assure equal efficacy and improve overall disease-free survival.

WITH THE ADVENT of effective combination chemotherapy, children with acute lymphoblastic leukemia (ALL) were noted to experience prolonged hematologic remissions. However, these remissions were interrupted in up to 65% of patients by the emergence of CNS leukemia, which frequently heralded subsequent systemic relapse. In the early 1960s, several programs were designed to eradicate subclinical foci of meningeal disease. These programs utilized intrathecal methotrexate (i.t. MTX) either alone or in combination with cranial irradiation or craniospinal irradiation. The efficacy of CNS prophylaxis (CNSP) has been an important variable in improving long-term disease-free survival in childhood ALL.

Although the acute complications of CNSP are similar regardless of technique, much controversy and uncertainty surround the long-term sequelae of CNSP. Delayed effects attributed to CNSP include neuroendocrine abnormalities, neuropsychologic and intellectual impairment, leukoencephalopathy, and abnormal computed tomography of the brain. We report on the efficacy and morbidity of CNSP with cranial irradiation and i.t. MTX in children with ALL treated at Children’s Hospital Medical Center, Sidney Farber Cancer Institute and the Joint Center for Radiation Therapy between 1972 and 1979.

MATERIALS AND METHODS

Two-hundred twenty-seven children with untreated ALL ages 1 mo to 15 yr attained complete remission between August 1972 and December 1979. The children were treated on four separate studies (Table 1), the results of which are summarized in Table 2 and Fig. 1. Twelve children manifested clinical or cytocentrifuge evidence of CNS leukemia prior to scheduled CNSP and will be discussed as a separate group because, by definition, overt CNS leukemia could not be prevented. One child who relapsed in the CNS after receiving only i.t. MTX as part of an early randomized study was included in the overall results (Tables I and 2) but was excluded from CNS disease-free results (Fig. 2) because her CNS relapse was not a consequence of the failure of cranial irradiation.

The initial features of the 215 children who had no evidence of CNS disease at diagnosis are shown in Table 3. Forty-two patients (20%) had a white blood count (WBC) greater than 50,000/cu mm, 73 patients (34%) were in an unfavorable age group (<2 or 9-15 yr), and 16 patients (7%) had T-cell ALL. Lumbar punctures were initially performed at the time of presumed complete remission unless clinical signs or symptoms necessitated earlier intervention. Two-hundred and five children received identical CNSP consisting of i.t. MTX plus cranial irradiation consisting of 2400 rad in 13 fractions over 2.5 wk utilizing a 4 MEV linear accelerator. All meningeal surfaces of the brain and upper cervical spinal canal to the inferior level of the second cervical vertebra were fully irradiated. From 1972 to 1977 i.t. MTX 12 mg/sq m (with a maximum dose of 12 mg after July 1974) was given via a lumbar puncture 4-5 times during cranial radiation and every 1 wk during continuation therapy. Beginning in 1978, the dose was changed to 12 mg/dose for patients age 3 yr and older, 10 mg for those 2-3 yr, 8 mg for those 1-2 yr, and 6 mg for those under 1 yr. More than 95% of the children received their cranial irradiation at the Joint Center for Radiation Therapy using identical fields, techniques, and equipment. Ten children on protocol 72-01 initially received only i.t. MTX as part of a randomized study to compare i.t. MTX and cranial

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ALL DISEASE-FREE SURVIVAL 1972-01

Fig. 1. Disease-free survival for 215 children with ALL treated from 1972 to 1979. All chemotherapy was stopped after 30 mo in continuous complete remission. DFS, disease-free survival.

Table 1. Summary of Therapy Regimens

<table>
<thead>
<tr>
<th>Protocol</th>
<th>N</th>
<th>Induction</th>
<th>Maintenance Chemotherapy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>72-01</td>
<td>30</td>
<td>VP + ASP</td>
<td>ADR, 6MP, MTX, VP</td>
<td>22</td>
</tr>
<tr>
<td>73-01</td>
<td>119</td>
<td>VP + ADR or DNR</td>
<td>ADR, 6MP, MTX, VP</td>
<td>23</td>
</tr>
<tr>
<td>77-01</td>
<td>68</td>
<td>VP ADR</td>
<td>ADR, 6MP, MTX, VP, + ASP</td>
<td>24</td>
</tr>
<tr>
<td>T-Cell</td>
<td>10</td>
<td>VP ADR</td>
<td>ADR, ARA-C, CTX, VP</td>
<td>25</td>
</tr>
</tbody>
</table>

VP, vincristine and prednisone; ASP, asparaginase; ADR, adriamycin; DNR, daunorubicin; 6MP, 6-mercaptopurine; MTX, methotrexate; CTX, cyclophosphamide; ARA-C, cytosine arabinoside.

Table 2. Results of Therapy Protocols 72-01, 73-01, 77-01, and T-Cell

<table>
<thead>
<tr>
<th>Protocol</th>
<th>72-01</th>
<th>73-01</th>
<th>77-01</th>
<th>T-Cell</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients*</td>
<td>30</td>
<td>112</td>
<td>64</td>
<td>9</td>
<td>215</td>
</tr>
<tr>
<td>Number in continuous remission</td>
<td>14</td>
<td>54</td>
<td>41</td>
<td>2</td>
<td>111</td>
</tr>
<tr>
<td>Median follow-up (mo)</td>
<td>103</td>
<td>71</td>
<td>33</td>
<td>(40+, 41+)</td>
<td></td>
</tr>
<tr>
<td>Remission deaths</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Relapse†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td>12 (1)</td>
<td>55 (19)</td>
<td>19 (2)</td>
<td>3</td>
<td>89 (22)</td>
</tr>
<tr>
<td>BM</td>
<td>11 (1)</td>
<td>45 (14)</td>
<td>13 (1)</td>
<td>3</td>
<td>72 (16)</td>
</tr>
<tr>
<td>CNS</td>
<td>1†</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Testicle</td>
<td>0</td>
<td>6 (5)</td>
<td>1 (1)</td>
<td>0</td>
<td>7 (6)</td>
</tr>
<tr>
<td>BM + CNS</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>BM + CNS + testicle</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CNS + testicle</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Electively off therapy</td>
<td>15 (1)</td>
<td>73 (19)</td>
<td>25 (2)</td>
<td>2</td>
<td>115 (22)</td>
</tr>
</tbody>
</table>

BM, bone marrow; CNS, central nervous system.

*All patients (n = 12) with CNS leukemia prior to scheduled CNS prophylaxis are excluded (see text for details).
†Numbers in parentheses represent children who relapsed after elective cessation of therapy.
‡This patient initially received intrathecal methotrexate only.

irradiation.27 Seven of the 10 children subsequently underwent reprophylaxis using cranial irradiation and i.t. MTX.

Maintenance chemotherapy is shown in Table 1 and varied slightly between protocols. It should be noted that, in general, drugs were administered every 3 wk as 5-day “pulses” (as opposed to more standard regimens wherein “continuous” chemotherapy is the rule).

The effects of CNSP were analyzed in three periods: during and shortly after cranial irradiation (acute effects), during continuation therapy, and after therapy was stopped (late effects). All acute effects, except somnolence, were assessed from the time of initiating CNSP through a period ending 3 wk from its completion. The CNSP somnolence syndrome,27 defined as lethargy, irritability, and/or sleepiness, with or without fever, was assessed through a period ending 8 wk after the completion of CNSP. All patients underwent ophthalmologic examinations at the end of therapy and at yearly intervals if cataracts were noted. Information about hair change following cessation of therapy was noted at the time of follow-up examination and confirmed by parents. Assessment of school performance was made by clinic personnel and through questionnaires sent to parents and school teachers. Specific areas investigated included attention span, motivation, memory, school achievement, social and/or emotional adjustment. Any child who was judged below average in one or more parameter by one or more source was considered at high risk of having or developing a learning disability. Neuropsychologic evaluation consisted of Weschsler Intelligence Scale for Children, Revised Version (WISC-R), and tests of language, visual-motor, and fine motor skills, as well as academic achievement.

RESULTS

Of the 215 children evaluated, 15 died in remission from infection and/or drug-induced cardiomyopathy; 89 relapsed; and as of July 1981, 111 children remained in continuous complete remission (CCR) from 20+ to 106+ mo (median follow-up 65 mo). Eighteen of the 111 children continued to receive chemotherapy. A total of 115 patients had therapy stopped after 30 mo of CCR. Sixty-seven relapses occurred during therapy and 22 were after elective cessation of drugs. Figure 1 illustrates the overall disease-free survival for all 215 children.
Of the 115 children whose therapy was electively discontinued, 93 remained in CCR from 30+ to 106+ mo (median 79 mo). Sixty-nine of these patients, who had a minimum follow-up of 4 yr, comprise the group who were evaluated for late effects of CNSP. Analysis of the features at diagnosis of the 69 patients evaluable for late effects revealed that at the time of diagnosis 17 (25%) were in the unfavorable age group, 9 (13%) had a WBC greater than 50,000/cu mm, and one had T-cell disease.

Of the 89 relapses, 72 were in the bone marrow only and 17 at other sites (with or without marrow involvement). Excluding the one child who received CNSP with only i.t. MTX, five relapses occurred in the CNS only, seven in the testis, two in the marrow and CNS, one in the marrow, CNS, and testis, and one in the CNS and testis (Table 2).

Thus, failure of prophylactic cranial irradiation and i.t. MTX, as manifested by primary CNS leukemia, was seen in 5 patients, and as CNS leukemia and another concomitant site of relapse in 4 other patients. Therefore, CNS leukemia appeared in a total of 9 children (4%). Figure 2 illustrates overall CNS disease-free survival. Pertinent clinical features of the nine children who developed CNS relapses are presented in Table 4. Of the five children who developed primary CNS relapse, all initially had WBCs >50,000/cu mm, two were in an unfavorable age group, none had T-cell disease, and one patient received inadequate irradiation fields at another hospital. Of the four children with concomitant CNS and other site relapse, three had initial WBCs >50,000/cu mm.
Three were in an unfavorable age group, and two had T-cell disease.

Twelve children, two boys and ten girls, had cytologic evidence of CNS leukemia, with or without clinical signs and symptoms, prior to the scheduled onset of CNSP. They ranged in age from 1 mo to 13 yr (median age 6 yr), and only three of them were in the unfavorable age group. Two of the patients had T-cell ALL. All of the children received i.t. MTX until there was no evidence of lymphoblasts in the cerebrospinal fluid. Eleven of them were then treated with cranial irradiation consisting of 2800 rad and 4–5 subsequent concurrent doses of i.t. MTX. The other child, a 3-mo-old, received only intraventricular chemotherapy and no radiation. Seven of the 12 children relapsed: two in the bone marrow, two in the CNS, and three in the bone marrow and CNS simultaneously. Five of the patients remained in CCR between 30+ and 88+ mo. Two of them, both of whom were less than 5 yr old at the time of CNS therapy, have documented learning disabilities.

**Acute Effects of CNSP (Table 5)**

Immediate minor toxicity included headache (32%), arachnoiditis (nausea, vomiting, nuchal rigidity, back pain) (22%), mucositis (27%), somnolence (45%), and delay or decrease in systemic chemotherapy (46%). Major acute toxicity included seizures in seven patients (3%) and life-threatening infections in seven patients (3%). The seizures all occurred within 8 wk of completing CNSP. Although i.t. MTX was administered throughout continuation therapy, no seizures occurred during this time. Infections included meningitis, sepsis, and pneumonia and were fatal in one child.

**Late Effects**

Of 69 children evaluable for late effects, 34 (50%) developed posterior subcapsular cataracts. (One of these children had had a congenital cataract.) The subcapsular cataracts were small, did not grow, impair vision, nor require any surgery. Sixty-one children (88%) had hair changes characterized by thinning, partial alopecia (especially at the top of the head), finer texture than before CNSP, and/or changes in color. Some of these hair findings appeared to gradually improve over prolonged periods (5 yr or more).

Sixty-six of the 69 children were regularly attending school at the time of evaluation, two were too young to be in school and one was kept at home because of longstanding cerebral palsy since birth. Of the 66 children in school, 54 (82%) were reported by their teachers or parents to have normal school performance. Twelve others (18%) met our criteria to have or be at risk of developing a learning disability. Nine of the 12 children underwent neuropsychologic evaluation, but none of the 57 remaining children were tested. All nine children showed selective deficits in one or more of the tests that required sustained attention and the ability to organize an output response, whether motor, drawn, or verbal. This is a pattern often encountered in children with an attention deficit disorder.

The mean of Full Scale, Verbal Scale, and Performance Scale IQs on the WISC-R were all within the average range. The distribution of scores on each of these scales ranged from low average to superior. On the neuropsychologic tests, between 66% and 100% scored at age level or better on tests of receptive language, memory for sentences, memory for stories, and the ability to use grammar, but five of nine children scored 1 yr or more below age expectation on a word retrieval test (Boston Naming). Eight of nine children scored 1 yr or more below age level on tests involving copying simple (Beery VMI) or complex (Rey Figure) abstract design, which measure visual motor abilities. Six of seven children showed significant slowing or inaccuracies of performance on the Timed Motor Exam or grooved Peg Placing Tests, both measures of fine motor coordination. On the Wide Range Achievement Test only one child tested below grade level on reading or spelling, while three of seven scored below grade level on arithmetic. Arithmetic was lowest of the three scores (reading, spelling, arithmetic) for five of seven children.

Comparison of the features of the children with learning disabilities and those with normal school performance revealed a high male to female ratio (2:1 versus 1:2:1) and a younger median age at diagnosis (3 yr versus 6 yr) in the former group. Of the 31 evaluable children younger than 5 yr at diagnosis, 11 (35%) were in the group who developed or were at high risk for developing a learning disability, whereas only one of 35 children who were 5 yr or older at diagnosis were at risk and developed a learning disability (p = 0.0008, Fisher exact test).
CNS PROPHYLAXIS IN ALL

DISCUSSION

CNSP with cranial irradiation and i.t. MTX in 214 children resulted in a 2% incidence of primary meningeal relapse. All CNS relapses were in a high risk group (WBC >50,000/cu mm, age <2 or >9 yr, and/or T-cell ALL). Moreover, cranial irradiation (2800 rad) and i.t. MTX were successful in the treatment of CNS leukemia present at diagnosis or prior to scheduled CNSP in 7 of 11 patients. Thus, it was possible to successfully treat children who initially had CNS involvement. Our practice of performing initial lumbar punctures at the time of presumed complete remission, after treatment with prednisone, would tend to underestimate the incidence of CNS leukemic involvement present prior to CNSP.

Such a low frequency of primary meningeal relapse after a relatively long follow-up (median of 5 yr) has not been paralleled in any published series. Haghin and coworkers, using i.t. MTX and intensive 8-drug systemic therapy without cranial irradiation, reported a 7% (9/127) incidence of primary CNS relapse. Using a combination of cranial irradiation and intrathecal methotrexate, aur and coworkers noted a 9% (21/228) incidence of primary meningeal leukemia. Australian investigators, utilizing CNSP similar to ours in combination with BCG innoculation and intermittent systemic chemotherapy, reported primary meningeal relapse in 4 of 28 children (14%).

Green and coworkers retrospectively compared three modalities of CNS prophylaxis: (1) i.t. MTX, (2) cranial irradiation and i.t. MTX (including 103 patients also reported here), and (3) intermediate dose intravenous methotrexate and i.t. MTX. They found a significantly lower incidence of primary CNS relapse in the group of patients who received cranial irradiation and i.t. MTX as compared to the other two groups. In addition, the overall disease-free survival was improved for increased risk children who had received cranial irradiation. A more recent update of that comparative experience suggested that there was no difference in disease-free survival for standard risk patients treated with either intermediate dose intravenous methotrexate or cranial irradiation plus i.t. MTX.

The difference observed in primary meningeal relapse rates between our patients and those in other series treated with the same modality of CNSP may be accounted for by differences in radiation technique. For example, failure to include all meningeal surfaces within the therapy portal could result in inadequate control. Another possible explanation for the success in prevention of CNS leukemia may be related to the use of i.t. MTX every 18 wk during continuation therapy. It is of note that there has not been a single CNS relapse among our standard risk children (age 2–9 yr and WBC <20,000/cu mm); nor have any children developed primary CNS relapse following cessation of chemotherapy. Despite the superiority of our program in preventing CNS leukemia, the overall disease-free survival for all patients combined was comparable to that of other groups. Therefore, we are currently directing attention to improving the efficacy of systemic chemotherapy.

The immediate complications of this CNSP program were similar in both type and incidence to those in other published series. No correlation was found between the development of somnolence and/or seizures and the occurrence of neurologic deficits or learning disabilities at a later stage. In addition, no encephalopathy was observed.

With increasing long-term disease-free survival of children treated for ALL, much concern has been directed to the potentially unfavorable late sequelae of therapy. The controversy surrounding late effects of CNSP emanates, in part, from the difficulty in separating the sequelae of systemic chemotherapy from those of CNSP. For example, the development of small, visually nonimpairing posterior, subcapsular cataracts in 50% of our population cannot be solely attributed to CNSP. It has been reported that systemic steroids can induce similar cataracts in up to 40% of patients. The hair changes that we observed have not been previously reported. Partial or total alopecia is very frequent during or shortly after irradiation and is usually reversible. Whether the hair changes noted after cessation of therapy were attributable to cranial irradiation only, to its combination with systemic adriamycin, or to technical features was unclear. However, as changes of this frequency and degree are not reported in children treated to high doses of cranial irradiation for primary CNS neoplasms, we suspect that a chemotherapy–irradiation interaction, perhaps between irradiation and adriamycin, was responsible.

Clearly, a major concern of those who care for long-term survivors of antileukemic therapy is the effect of treatment on intellectual and scholastic performance. To date, the few studies assessing such performance reveal major inconsistencies and often lack well controlled comprehensive evaluation with appropriate follow-up. One report of 18 children tested before and then at least 3 yr after CNSP with cranial irradiation and i.t. MTX showed a statistically significant decrease in IQ scores between the initial and final testing. This same study also found neuropsychologic deficits in the majority of irradiated patients. Unfortunately, comparisons with an ALL “control” group treated without cranial irradiation could not be made because the latter patients were not tested before and after CNSP and had also received different systemic
therapy. Moreover, some irradiated patients were tested while presumably still receiving therapy, whereas the control group was tested several years after the cessation of treatment. This difference may be of clinical importance. German investigators have reported improvement in neuropsychologic function after the cessation of therapy.47

In another study, McIntosh and coworkers delineated significant abnormalities on gross and fine motor, perceptual, language, or behavioral function in 8 of 23 children.16 Other investigators found no difference in intellectual performance between older children (>5 yr) treated with cranial irradiation and their matched controls; however, younger children (<5 yr) tended to perform below their matched controls in tasks measuring quantitative, memory, and motor skills.12 Subsequently, these same investigators reported lower scores in all general psychologic measures in children with leukemia compared to normal controls and to a group of children with solid tumors treated without cranial irradiation.48 Differences were significantly greater between the younger children with leukemia and controls. Similar findings have been reported by investigators at the National Cancer Institute.14 Their data suggested that CNSP may adversely influence intellectual development, especially in young children.

Verzosa and coworkers found no abnormalities in performance after treatment with cranial irradiation and i.t. MTX.45 They assessed social adjustment, behavior, and intellectual performance in 22 children who were off therapy for 5 yr; all had normal neuropsychologic performance. Later investigations from the same institution demonstrated different conclusions.15 They found that young patients were at increased risk for development of neuropsychologic dysfunction. Tamaroff and coworkers49 observed no significant difference in the performance of children with ALL whose CNSP consisted of only i.t. MTX and a matched group with rhabdomyosarcomas who received no CNSP. The percentage of learning disabilities in each group was similar (16% and 18%) and comparable to that encountered in a normal community (16%),50 as well as in our questionnaire-screened patient population (18%). Neuropsychologic testing within our population was not performed in the 80% of patients who were functioning at age-appropriate school grade level and who had no reported behavioral problems. It is conceivable that such testing might uncover abnormalities, or that they may appear at a later age. Careful sequential follow-up of scholastic performance must be done on all long-term survivors of leukemia therapy.

Another possible explanation for the absence of functional intellectual losses (as manifested by age-appropriate grade level in school) may be related to maintenance chemotherapy. It has been shown that intravenous methotrexate administered after cranial irradiation can result in CNS toxicity.40 In our treatment protocols, maintenance therapy excluded methotrexate (except i.t. MTX) during the first year following CNSP. It is possible that the hiatus between cranial irradiation and the introduction of systemic methotrexate resulted in relative sparing of brain toxicity.

The goal of any CNSP modality must be prevention of CNS leukemia. The devastating impact of a CNS relapse on subsequent hematologic relapse and on survival cannot be overemphasized.51

We conclude that the combination of cranial irradiation and i.t. MTX was highly efficacious. The acute and late morbidity of such treatment as demonstrated in this patient population would support its continued use. However, the high incidence of learning disabilities in patients less than 5 yr old, as well as a report of second malignant neoplasms within irradiation fields in another patient population,52 are disturbing and necessitate continuous reevaluation of alternative treatment modalities. Future programs should attempt to decrease morbidity, but must also assure equal efficacy and improve overall disease-free survival.

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Efficacy and morbidity of central nervous system "prophylaxis" in childhood acute lymphoblastic leukemia: eight years' experience with cranial irradiation and intrathecal methotrexate

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