Central Nervous System Leukemia in Children with Acute Nonlymphoblastic Leukemia

By Ching-Hon Pui, Gary V. Dahl, David K. Kalwinsky, A. Thomas Look, Joseph Miro, Richard K. Dodge, and Joseph V. Simone

Factors contributing to the development of central nervous system (CNS) leukemia, and the impact of leukemic involvement of this site on subsequent remission length, were determined in 184 children with acute nonlymphoblastic leukemia who had been treated in two successive clinical trials. Preventive CNS therapy in both studies consisted of intrathecal methotrexate (12 mg/m²) given monthly during the first six months of therapy and then every three months until all treatment was stopped. Children with CNS leukemia at diagnosis or relapse were given intrathecal chemotherapy weekly for four weeks and then monthly throughout the remainder of the treatment course. Those continuing in complete remission received preventive CNS therapy in both studies were determined in 184 children with acute nonlymphoblastic leukemia (ANLL) than in those with acute lymphoblastic leukemia (ALL). Although the CNS has not been considered a major site of initial relapse in ANLL, the frequency of this complication appears to be increasing with improved survival times. Indeed, after adjustment for time at risk, CNS relapse occurs as often in ANLL as in ALL. Despite these observations, the role and optimal method of CNS prophylaxis in ANLL remains controversial.

In an earlier study at St Jude Children's Research Hospital, craniospinal irradiation proved to be an effective method for preventing meningeal leukemia in patients with ANLL, but such treatment had no apparent impact on the quality or duration of subsequent survival. Chemotherapy was poorly tolerated, most likely because of decreased marrow reserves but such treatment had no apparent impact on the quality or duration of subsequent survival.

MATERIALS AND METHODS

One hundred eighty-seven consecutively previously untreated patients <20 years of age with ANLL were admitted to two clinical trials (AML-76 and AML-80) from January 1976 to October 1983 at St Jude Children's Research Hospital. ANLL was diagnosed when >25% of the cells infiltrating the bone marrow were leukemic and showed myeloid, monocytic, promyelocytic, or erythroid differentiation, as determined by morphological and cytochemical examination. Cell types were classified according to French-American-British (FAB) criteria after study of bone marrow smears stained with Wright's-Giemsa, periodic acid-Schiff reagent, Sudan black B, myeloperoxidase, naphthol AS-D chloroacetate esterase, α-naphthyl acetate esterase and α-naphthyl butyrate esterase. Bone marrow aspirates were examined routinely every three months during treatment or at any time relapse was suspected.

CNS leukemia was diagnosed when leukemic blasts were identified in Wright's-stained cytospin centrifuged samples of cerebrospinal fluid (CSF) by at least two observers, when there were clinical signs of increased intracranial pressure and cranial nerve palsy, or when there was a nonhemorrhagic intracerebral mass disclosed by computed tomography. If the cellular morphology was questionable or ie, the CSF was contaminated by blood (>10 erythrocytes/μL) containing leukemic blasts, a second sample was obtained a few days later. CSF was examined at diagnosis and each time when a lumbar puncture was performed to instill intrathecal methotrexate.

All investigations were approved by the institution's clinical trials committee; informed consent was obtained for all patients.

TREATMENT. The two treatment protocols have been described elsewhere. In brief, for patients in the AML-76 study, remission induction therapy consisted of weekly daunorubicin (25 mg/m²), vincristine (1.5 mg/m²), 6-azauridine (15 g/m² × 3), and cytarabine (150 mg/m² × 4) for up to six weeks. Monthly vincristine, doxorubicin, cyclophosphamide, and weekly cytarabine and 6-mercaptopurine were used for continuation therapy. Late intensive therapy (prednisone, vincristine, methotrexate, and 6-mercaptopurine) was administered to all patients in remission on months 31 and 32 before cessation of chemotherapy.

In the AML-80 study, remission induction consisted of daunorubicin (45 mg/m² × 3) and cytarabine (100 mg/m²/d in a single continuous infusion × 7) with an additional course given if marrow...
hypoplasia was not achieved. Remissions were maintained with sequential intensive chemotherapy consisting of different drug pairs administered for 15 months: doxorubicin and cytarabine, etoposide and 5-azacytidine, 6-thioguanine, and cytarabine.

Preventive CNS therapy was identical in the two protocols. Intrathecal methotrexate (12 mg/m², maximum 15 mg) was given each month during the first six months of treatment and then every three months until all therapy was stopped. If CNS leukemia was present at diagnosis, developed during remission induction, or developed while patients were in initial hematological remission, intrathecal methotrexate (with added cytarabine for two patients with initial CNS leukemia and subsequent CNS relapse) was given weekly for four weeks and then monthly throughout the remainder of therapy. Any patient who was successfully treated for CNS leukemia at diagnosis or for CNS relapse and then remained in remission until the end of continuation therapy received 2,400 rad cranial irradiation with five doses of intrathecal methotrexate before cessation of chemotherapy.

Statistical analysis. The chi-square test for contingency tables was used to compare differences in the distribution of clinical features or remission induction rates between patients with or without CNS leukemia at diagnosis. The Kaplan-Meier procedure was used to estimate the proportion of patients in remission; the resulting curves were compared by the Cox-Mantel test. The latter two methods were used to compare the complete remission durations for patients with or without CNS involvement at diagnosis and the CNS remission durations among discrete groups of patients. For analysis of CNS remission durations, patients who died or had other forms of relapse were censored at the time of the adverse events.

The influence of potential prognostic factors on time to CNS relapse and the effect of CNS leukemia at diagnosis on time to failure were estimated with the Cox proportional hazards model. The variables tested included age, leukocyte count, liver and spleen size, platelet count, hemoglobin level, coagulopathy, sex, race, FAB type, and CNS leukemia at diagnosis. Each factor was first tested as a single regressor variable in the Cox model (univariate analysis). A stepwise multivariate regression approach was then used to identify the most important predictor variables with respect to time to CNS relapse. A P value of ≤.10, after adjustment for the effects of other variables, was required for retention in the "best" model.

RESULTS

Of the 187 children enrolled in the studies, 184 had CSF examinations at diagnosis and were eligible for analysis. The three patients who were not evaluated died shortly after admission, before the initiation of chemotherapy, and hence did not have lumbar punctures performed. Thirty-five children were found to have CNS leukemia before induction treatment, and three developed it during induction prior to administration of the first intrathecal therapy; thus, 38 (20.7%) of 184 patients were considered to have CNS leukemia at diagnosis. CNS leukemia was diagnosed on the basis of demonstrable leukemic blasts in CSF in 35 patients, the presence of an intracerebral mass in 2, and multiple cranial nerve palsies in 1.

There were 22 boys and 16 girls, with a median age of 4.8 years (range, 2 months to 19 years). At presentation, chloromas were also identified in 8 patients, retinal hemorrhage or infiltration in 4, cranial nerve palsy in 4, and meningeal signs in 1. The presenting clinical and laboratory features of this group are listed in Table 1.
lacking CNS involvement, these children were more likely to have an initial leukocyte count ≥25 × 10⁹/L (P = .01) and age <2 years (P = .03). There was no correlation between initial CNS leukemia and race, hemoglobin level, spleen size, sex, FAB type, coagulation abnormalities, liver size, or platelet count. For the 38 patients, CSF leukocyte counts ranged from 1 to 183/µL (median, 6), levels of CSF protein from 6 to 54 mg/dL (median, 19) and glucose levels from 49 to 123 mg/dL (median, 68). Only three patients required two weekly doses of intrathecal methotrexate to clear blasts from the CSF; the remainder had no demonstrable blasts in their CSF after a single intrathecal treatment.

The presence of CNS leukemia at diagnosis did not affect treatment outcome. Thirty-two of the 38 patients with CNS leukemia, compared with 106 of 146 without such involvement, achieved a complete remission (P = .13). Durations of complete remission for the two groups were similar (P = .73, Fig 1). By Cox multivariate analysis, the influence of this factor on time to failure was again negligible (data not shown).

Asymptomatic CNS relapse, found during routine follow-up, ended initial complete remissions in 11 children, whose clinical data are summarized in Table 2. Seven patients were <2 years of age; 9 had leukocyte counts ≥25 × 10⁹/L; 9 had monocytic (M5) or myelomonocytic leukemia (M4); and 5 had had CNS leukemia at diagnosis. Initial remission durations ranged from 1 to 46 months. At the time of relapse, the CSF blast cell counts ranged from 1 to 395/µL; levels of CSF protein and glucose were normal in all patients. Four patients are off therapy and in subsequent remission for 33+ to 78+ months following a CNS relapse; one of them, despite a second CNS relapse, is off therapy and in remission for 54+ months.

By the Cox-Mantel test,19 four features at diagnosis were found to predict a CNS relapse: age <2 years (P = .001), M4 or M5 morphology (P = .002), leukocyte count ≥25 × 10⁹/L (P = .012), and presence of coagulopathy (P = .015) (Table 3). The presence of CNS leukemia at diagnosis, although not achieving statistical significance, appeared to be associated with subsequent CNS relapse.

Because children <2 years of age and those with initial leukocyte counts ≥25 × 10⁹/L were more likely to have M4 or M5 leukemia (P = .001 and 0.006, respectively), these risk factors appear to be interrelated. Thus, stepwise Cox regression analysis was used to identify the most important variables with respect to time to CNS relapse. By this approach, age <2 years, initial leukocyte count ≥25 × 10⁹/L, and M4 or M5 morphology were each found to have independent predictive value, by virtue of their retention in the "best" model (Table 4).

Because the criteria for diagnosis of CNS leukemia differ among treatment centers, we also analyzed our findings according to guidelines of the Childrens Cancer Study Group: nucleated cell counts ≥5/µL in CSF with identifiable leukemic blasts, presence of cranial nerve palsy or intracranial choroma (Bleyer WA, personal communication). By these criteria, 24 (13%) of 184 patients were considered to have CNS leukemia at diagnosis. The CSF leukocyte counts ranged from 5 to 183/µL (median, 18). Two patients required two doses of intrathecal methotrexate for eradication of blasts from CSF, whereas the others required only one dose. Initial CNS leukemia was associated with age <2 years but not with other clinical or laboratory features. Of 35 children <2 years of age, 9 presented with CNS leukemia, compared with 15 of 149 older children (P = .02). Neither remission induction rate (P = .45) nor remission duration (P = .74) was adversely affected by the presence of CNS leukemia at diagnosis. Four of 20 children with initial CNS involvement who achieved remission subsequently had a CNS relapse, in contrast to only 7 of the 118 without initial CNS leukemia (P = .05). By stepwise Cox regression analysis, however, the risk factors associated with CNS relapse remain the same: age <2 years, initial leukocyte count ≥25 × 10⁹/L, and M4 or M5 morphology.

**DISCUSSION**

The criteria for diagnosis of initial CNS leukemia in children with ANLL have not been well defined, and reported frequencies of this involvement range widely: 4.8%;14 7%;16 9%;17 14%;12 and 19.3%. The 20.7% finding in the present series is high, but is similar to that in our previous study1 and to the 18% reported by Meyer et al for adults.18 This discrepancy may be attributable in part to improved cytological preparations for detection of leukemic blasts and to less conservative criteria for the diagnosis of CNS leukemia. We consider the presence of leukemic blasts in a cytocentrifuged preparation of uncontaminated CSF as definitive evidence of CNS involvement, even though the mononuclear cell count is <5/µL. With use of criteria of the Childrens Cancer Study Group, the frequency of initial CNS leukemia in this series decreases to 13%.

Baehner et al15 reported that in their study all 11 children with CNS disease had leukocyte counts >75 × 10⁹/L, and nine had blast cells with M4 or M5 morphology. Meyer et al18 noted M4 blast morphology for each of their seven adult patients who, as a group, had higher leukocyte counts and serum lysozyme levels with an increased frequency of splenomegaly and other extramedullary involvement. Similarly, Creutzig et al19 found that 26% of their patients with M4 blasts, as compared to 3% of those with other subtypes, had CNS leukemia at diagnosis. In our series, children with CNS leukemia...
Table 2. Clinical Data for Patients With a CNS Relapse

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Initial Leukocyte Count (\times 10^9/L)</th>
<th>FAB Type</th>
<th>Initial CNS Leukemia</th>
<th>Duration of First Remission (mo)</th>
<th>CSF Leukocyte Count at Relapse (per (\mu L))</th>
<th>Intrathecal Treatment</th>
<th>Subsequent Relapse</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mo</td>
<td>F</td>
<td>295</td>
<td>M2</td>
<td>No</td>
<td>1</td>
<td>8</td>
<td>MTX</td>
<td>No</td>
<td>CR 78 + mo</td>
</tr>
<tr>
<td>2</td>
<td>1 yr, 2 mo</td>
<td>F</td>
<td>88</td>
<td>M5</td>
<td>No</td>
<td>19</td>
<td>395</td>
<td>MTX</td>
<td>No</td>
<td>CR 58 + mo</td>
</tr>
<tr>
<td>3</td>
<td>5 mo</td>
<td>F</td>
<td>25</td>
<td>M5</td>
<td>No</td>
<td>10</td>
<td>100</td>
<td>MTX</td>
<td>CNS relapse (4 mo later)</td>
<td>CR 54 + mo</td>
</tr>
<tr>
<td>4†</td>
<td>2 yr, 3 mo</td>
<td>M</td>
<td>5</td>
<td>M4</td>
<td>No</td>
<td>46</td>
<td>11</td>
<td>MTX</td>
<td>No</td>
<td>CR 33 + mo</td>
</tr>
<tr>
<td>5</td>
<td>8 mo</td>
<td>F</td>
<td>117</td>
<td>M4</td>
<td>Yes</td>
<td>3</td>
<td>2</td>
<td>MTX</td>
<td>CNS → Hematological relapse (9 mo later)</td>
<td>Died in 19 mo</td>
</tr>
<tr>
<td>6</td>
<td>4 yr, 4 mo</td>
<td>M</td>
<td>295</td>
<td>M5</td>
<td>No</td>
<td>1</td>
<td>34</td>
<td>MTX</td>
<td>Hematological + CNS relapse (15 mo later)</td>
<td>Died in 16 mo</td>
</tr>
<tr>
<td>7</td>
<td>1 yr</td>
<td>M</td>
<td>12</td>
<td>M4</td>
<td>Yes</td>
<td>1</td>
<td>3</td>
<td>MTX</td>
<td>2 CNS → hematological + testicular relapse (8 mo later)</td>
<td>Died in 9 mo</td>
</tr>
<tr>
<td>8</td>
<td>13 yr, 1 mo</td>
<td>M</td>
<td>440</td>
<td>M4</td>
<td>No</td>
<td>8</td>
<td>10</td>
<td>MTX</td>
<td>Hematological relapse (1 mo later)</td>
<td>Died in 7 mo</td>
</tr>
<tr>
<td>9</td>
<td>2 mo</td>
<td>M</td>
<td>70</td>
<td>M5</td>
<td>Yes</td>
<td>2</td>
<td>2</td>
<td>MTX + ara-C</td>
<td>Hematological relapse (6 mo later)</td>
<td>Died in 7 mo</td>
</tr>
<tr>
<td>10</td>
<td>1 yr, 10 mo</td>
<td>F</td>
<td>123</td>
<td>M5</td>
<td>Yes</td>
<td>11</td>
<td>1</td>
<td>MTX + ara-C</td>
<td>Hematological relapse (1 mo later)</td>
<td>Died in 5 mo</td>
</tr>
<tr>
<td>11†</td>
<td>13 yr, 2 mo</td>
<td>F</td>
<td>182</td>
<td>M1</td>
<td>Yes</td>
<td>5</td>
<td>1</td>
<td>MTX</td>
<td>No</td>
<td>Died in 2 mo</td>
</tr>
</tbody>
</table>

CNS, central nervous system; MTX, methotrexate; ara-C, cytarabine; CR, complete remission.
*CR refers to the duration of subsequent remission following a CNS relapse.
†Combined CNS and hematological relapse.
higher leukocyte counts (≥25 × 10^9/L) and age <2 years at diagnosis were more likely to have initial CNS leukemia. However, CNS leukemia at diagnosis was not correlated with FAB type: initial CNS involvement occurred in 18 of 68 children with M4 or M5 leukemia as compared with 19 of 108 children with other subtypes (P = .16).

The prognostic importance of CNS leukemia at diagnosis in ANLL is controversial. Although some investigators have linked this factor to a poorer outcome,1,2,13 others were unable to find a difference in the survival of patients with and without CNS involvement.16 By analyzing results for a much larger number of patients than has been included in other reported series, we have shown that CNS leukemia at diagnosis, if treated in the manner reported here, does not link this factor to a poorer outcome,13 a CNS relapse did not preclude long-term survival.

Several features identified at diagnosis were predictive of CNS relapse in this study. As reported by others,19-21 leukemic blast cells with either M4 or M5 morphology increased the risk of a CNS relapse. Nine of the 11 patients with CNS relapses had these FAB morphological subtypes. Additionally, age <2 years and leukocyte count ≥25 × 10^9/L were found to be associated with a higher relapse rate. Children with all three characteristics appear to have an especially high risk of treatment failure: five of ten such patients have already experienced a CNS relapse (P < .0001), in contrast to none of 45 who lacked these features.

Although the optimal method of CNS prophylaxis remains unknown, most recent clinical trials included this component of therapy as a means of prolonging complete remissions.5,15,17,22 In the VAPA-10 protocol, which secured good overall control of leukemia without use of specific CNS prophylactic therapy, 19 of the 45 children who achieved complete remission have relapsed, 8 in the CNS.19 Subsequent modification of the VAPA program incorporated intrathecal cytarabine for CNS prophylaxis. Craniospinal irradiation given early in remission is an effective prophylactic measure, but this method limits tolerance to chemotherapy and hence does not improve end results.1 Although cranial irradiation plus intrathecal methotrexate also appeared to be effective in preventing CNS relapse,17,23 it did not improve the duration of survival in one series,23 and its effect on overall remission duration could not be determined in the other series,17 as the study was not randomized for this treatment. Periodic intrathecal chemotherapy appears to be the logical choice to control the disease without undue effects on marrow reserves. Our study indicates that intermittent intrathecal methotrexate can be used to prevent or treat
CNS leukemia in most patients. Whether children lacking high-risk features require prophylactic CNS treatment must be studied further.

Similar to experience in ALL, the frequency of CNS relapse in ANLL is likely to increase with extended survival due to improved treatment. More effective CNS preventive therapy is needed for patients at high risk of CNS relapse. Eight of our 11 patients who relapsed in the CNS were <3 years of age, and their intrathecal methotrexate dosages were derived from body surface area. That the frequency of CNS relapse in young children with ALL may be significantly decreased by giving intrathecal methotrexate in dosages based on age rather than body surface area suggests that this approach should also be tried in ANLL. More frequent intrathecal treatment or addition of cytarabine to intrathecal methotrexate may further reduce the frequency of CNS relapse. Finally, high-dose cytarabine, which has been shown to be effective in the treatment of CNS leukemia and is a component of recently developed treatment regimens, may also be useful in the prevention of CNS relapse.

ACKNOWLEDGMENT

We thank J. R. Gilbert for his editorial review of the manuscript, and Ms Clara Mason and other staff of the leukemia-lymphoma division for dedicated patient care.

REFERENCES

Central nervous system leukemia in children with acute nonlymphoblastic leukemia

CH Pui, GV Dahl, DK Kalwinsky, AT Look, J Mirro, RK Dodge and JV Simone