Importance of Effective Central Nervous System Therapy in Isolated Bone Marrow Relapse of Childhood Acute Lymphoblastic Leukemia

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Presymptomatic central nervous system (CNS) treatment in children with a late isolated bone marrow (BM) relapse of acute lymphoblastic leukemia (ALL) was based on intermediate-dose systemic and intrathecal (IT) methotrexate (MTX) in the multicenter trial, ALL-REZ BFM 85. Because this was associated with an excess of overt second CNS relapses, cranial radiotherapy (cRT) plus prolonged triple IT therapy with MTX, cytarabine, and prednisone was instituted during the course of the subsequent trial, ALL-REZ BFM 87. Results of children with or without cRT, but otherwise identical chemotherapy, are presented here. Between April 1985 and March 1990, 93 children with their first late isolated BM relapse of ALL were entered on protocols ALL-REZ BFM 85M and ALL-REZ BFM 87. An intensive 6-month phase of multiagent chemotherapy that included MTX, cytarabine, and prednisone was followed by 2 years of conventional maintenance therapy with daily 6-thioguanine and biweekly MTX. Children with bone marrow transplantation excluded, 73 were in complete remission at the end of acute lymphoblastic leukemia (ALL) was based on intercranial irradiation (cRT) together with triple IT therapy to an unexpectedly high rate of second CNS relapses, “and findings during the course of trial ALL-REZ BFM 87. The introduction for children with negative cerebrospinal fluid results presented in the following report suggest this measure was associated with an excess of overt second CNS relapses, in reducing the overall relapse rate, and in increasing the overall survival rate.

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RADIOTHERAPY to the central nervous system (CNS) as treatment of subclinical meningeal infiltration has been successfully replaced by prolonged intrathecal (IT) chemotherapy with or without increased-dose systemic methotrexate (MTX) in a considerable proportion of children with newly diagnosed acute lymphoblastic leukemia (ALL). Salvage therapy protocols of isolated bone marrow (BM) relapse have been used with either periodic IT MTX (sometimes together with IT cytarabine and IT hydrocortisone) for 2 years in the Pediatric Oncology Group or systemic intermediate-dose MTX (1 g/m²) plus IT MTX administered 8 times during the first half-year of intensive chemotherapy in the BFM (Berlin-Frankfurt-Münster) Group. In trial ALL-REZ BFM 85, this was fraught with an unexpectedly high rate of second CNS relapses, and cranial irradiation (cRT) together with triple IT therapy to be administered in the second half-year of treatment was introduced for children with negative cerebrospinal fluid findings during the course of trial ALL-REZ BFM 87. The results presented in the following report suggest this measure to have effectively prevented second CNS relapses and to have substantially increased the overall probability of 6-year disease-free survival.

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PATIENTS AND METHODS

Children and adolescents up to 18 years of age with first relapse of non-B-ALL were enrolled in limb M (intermediate-dose MTX) of trial ALL-REZ BFM 85 (April 1985 to March 1987, n = 86) and ALL-REZ BFM 87 (April 1987 to March 1990, n = 182) after informed consent was obtained from the guardians. Late isolated BM relapses (more than 6 months after elective cessation of frontline therapy) accounted for 21 children in ALL-REZ BFM 85M and 72 children in ALL-REZ BFM 87. The duration of frontline therapy had been at least 18 months, with the exception of 1 girl in whom treatment had been stopped prematurely by the parents after 15 weeks. She relapsed 29 weeks later. In all other cases, frontline treatment was completed as planned. The vast majority of patients had been treated according to protocols featuring early multiagent intensification (BFM proper 65, modified BFM 9, CoALL 15).

All treatment protocols had been approved by the local ethical committee. The treatment strategy of trial ALL-REZ BFM 87 was a continuation of limb M of trial ALL-REZ BFM 85 (MTX 1 g/m² as 36-hour infusion) that has been described previously. At diagnosis, children received IT MTX (12 mg, reduced to 10 or 8 mg in children below 3 or 2 years of age, respectively), followed by prednisone (100 mg/m²) for 5 days, and then received alternating courses of polychemotherapy (R1 and R2, four courses each), as outlined in Table 1. Each course included IT therapy with MTX plus intermediate-dose systemic MTX (1 g/m² as continuous infusion over 36 hours). Maintenance therapy consisted of daily 6-thioguanine (50 mg/m²) and biweekly intravenous MTX (50 mg/m²) for 2 years.

Additional CNS prophylaxis, recommended for all ALL-REZ BFM 87 patients with BM relapse, consisted of cRT and prolonged triple IT therapy. After the end of intensive polychemotherapy (8 courses, approximately 6 months), cRT was performed in a fractionated fashion (1.7 Gy/d) at a dosage of 18 Gy, which was reduced to 12 Gy in children younger than 2 years of age and those who had received cRT during frontline treatment. After cRT, triple IT therapy was administered every 6 weeks until the end of the first year. Triple IT therapy consisted of MTX (12/10/8 mg), cytarabine (30/26/20 mg), and prednisone (10/8/6 mg) administered in an age-adapted fashion, with reduced dosages in children below 3 and 2 years of age.
The probability of disease-free survival (DFS) was calculated by the Kaplan-Meier method based on the time elapsed between the date of second complete remission (CR) and the date of an adverse event (second relapse; death in CR) or the last date the patient was reported to be in continuous complete remission (CCR). Subjects of this analysis were children who were in CR after the end of intensive polychemotherapy (6 months after diagnosis). Children who underwent BM transplantation (BMT) were excluded. Differences between treatment groups were assessed by the log-rank test.

RESULTS

Of 21 children with late isolated BM relapse of study ALL-REZ BFM 85M, 18 were in CR after the end of intensive polychemotherapy (6 months after diagnosis of relapse had been made), plus 1 child who underwent allogeneic BMT. These patients did not receive cRT. Similarly, 55 of 72 late isolated BM relapse patients of study ALL-REZ BFM 87 were in CR after completion of polychemotherapy courses, plus 9 children who underwent BMT. Of these 55 children, 15 patients were not irradiated for various reasons (parental refusal, n = 5; BMT planned but not performed, n = 4; local medical decision in children who had received cRT with 18 Gy or more in front-line protocols, n = 6); however, 11 of these 15 children received triple IT therapy during maintenance therapy. A total of 40 patients received triple IT and cRT therapy (21 children, 12 Gy; 18 children, 18 Gy; and 1 girl, 24 Gy). Thus, the total number of children with late isolated BM relapse who were in CR after completion of intensive polychemotherapy was 73. Of these, 40 children received full CNS prophylaxis with cRT, 11 did not receive cRT but prolonged triple IT therapy, and 22 received neither cRT nor prolonged triple IT therapy. Intensive polychemotherapy and maintenance therapy were otherwise identical for all children.

Of the 73 children analyzed, no patient had had CNS leukemia at first diagnosis. The 40 irradiated patients and the 33 children without cRT did not differ with respect to percentage of boys; age or BFM risk factor at first diagnosis of leukemia; employment of BFM or BFM-like front-line protocols; median duration of first remission; age, white blood cell count, or absolute peripheral blast count at diagnosis of relapse; immunologic phenotype; or percentage of BM blasts after 1 course of intensive chemotherapy (Table 2). However, 29 of 33 children who did not receive cRT for relapse treatment had been irradiated during front-line treatment, compared with only 20 of 40 children who were administered cRT during relapse treatment (P < .001). In patients who had received cRT during front-line treatment, the dosage of radiation administered initially had been similar in both groups (18 Gy or less, 20 of 29 patients and 16 of 20 patients, respectively).

The outcome of ALL-REZ BFM 85M and ALL-REZ BFM 87 children with late isolated BM relapse and children in CR after completion of intensive polychemotherapy is summarized in Table 3. Of 33 children without cRT, 26 relapsed, compared with 21 of 40 who had received cRT (P < .05). Relapses with overt BM involvement did not differ significantly between the two groups (17 of 33 vs 21 of 40).

Table 1. ALL-REZ BFM 85M and 87: Alternating Treatment Courses R1 and R2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administered on Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>100 mg/m²</td>
<td>PO</td>
<td>1-5</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>100 mg/m²</td>
<td>PO</td>
<td>1-5</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5 mg/m²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>MTX</td>
<td>1 g/m²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>MTX</td>
<td>12 (10/8) mg†</td>
<td>IT</td>
<td>1</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>300 mg/m²</td>
<td>IV</td>
<td>5</td>
</tr>
<tr>
<td>Teniposide</td>
<td>165 mg/m²</td>
<td>IV</td>
<td>5</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>10,000 U/m²</td>
<td>IV</td>
<td>6-8</td>
</tr>
</tbody>
</table>

Abbreviations: PO, by mouth; IV, intravenously; IT, intrathecally.
* IV MTX (1 g/m²) was administered over 36 hours, with subsequent low-dose leucovorin rescue (2 × 15 mg/m² at 48 hours and 54 hours after MTX start, or more if MTX serum levels are greater than 0.5 μmol/L at 48 hours after MTX start).
† IT MTX dose reduction in children below 3 and 2 years of age.

Table 2. Characteristics of Patients With Late Isolated BM Relapse Who Were in Remission After Completion of Intensive Therapy

<table>
<thead>
<tr>
<th>No cRT</th>
<th>cRT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>Boys</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>4.6 (1-14)</td>
<td>4.7 (2-14)</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BFM risk factor</td>
<td>1.11 (0.37-1.91)</td>
<td>0.70 (0.16-1.50)</td>
</tr>
<tr>
<td>Front-line protocols</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BFM</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Other early intensification</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>CNS irradiation performed</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Duration of 1st CR (mo)</td>
<td>42.4 (25-90)</td>
<td>28.2 (10-130)</td>
</tr>
<tr>
<td>Off therapy (mo)</td>
<td>19.5 (6-61)</td>
<td>17.6 (6-94)</td>
</tr>
<tr>
<td>At relapse</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>9.4 (5-16)</td>
<td>9.3 (4-17)</td>
</tr>
<tr>
<td>White blood cell count (no/L)</td>
<td>5,400 (1,300-48,900)</td>
<td>6,700 (1,800-79,800)</td>
</tr>
<tr>
<td>Absolute peripheral blast count</td>
<td>1,130 (0-40,460)</td>
<td>1,460 (0-70,220)</td>
</tr>
<tr>
<td>Common ALL (CD10+/cigM⁺)</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>BM blasts &gt;5% after 1st course</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

Values are the number of patients for categorical variables, and the median with the range in parentheses for numerical values.
However, relapses with CNS involvement occurred at a significantly higher rate in patients without cRT (10 of 33) than in patients who had received cRT (1 of 40; \( P < .01 \)). Twenty-one children without cRT died after relapse, compared with 12 irradiated patients \( (P < .01) \). At a median follow-up of 64 months (range 43 to 92 months), the estimated 6-year DFS rate of irradiated patients was .46, compared with .18 for children without cRT; \( P < .01 \) (Fig 1). Overall 6-year survival estimates after relapse were .68 in the cRT group and .31 for patients without cRT; \( P < .05 \).

Of the 11 non-cRT patients who had received triple IT during the first half-year of maintenance therapy, 2 were in CCR, compared with 4 of 22 non-cRT, non-triple IT-therapy children. The estimated 6-year DFS rates of both groups were indistinguishable (.14 v. .19; NS).

Because the proportion of children who did not receive cRT in retrieval therapy was significantly larger in the group of patients who were irradiated during front-line treatment than in the group without front-line cRT, children with and without front-line cRT were analyzed separately. In preirradiated patients, 10 of 20 children with second cRT are in CCR, compared with 6 of 29 without second cRT (6-year DFS rates, .48 v. .20; \( P < .05 \)). In patients without cRT during front-line therapy, 9 of 20 children with salvage cRT are in CCR (6-year DFS rate, .44), whereas all 4 children without salvage cRT relapsed.

For parental refusal, 1 girl had not completed front-line treatment as planned. She did not receive cRT during front-line therapy but during salvage therapy and is in CCR 69 months after relapse. Exclusion of this patient from data analysis did not result in any substantial changes.

An isolated seizure followed by reversible somnolence syndrome was reported in 1 irradiated patient. Transient somnolence, vomiting, and fatigue attributed to CNS irradiation were reported in 1 child in each group. Headache, vomiting, and fatigue (all reversible) were reported in a nonirradiated child during prolonged IT therapy. A boy with tuberous sclerosis, who also had not been irradiated but received intrathecal therapy, presented with a seizure, leading to the discontinuation of IT therapy. No encephalopathies were reported by the institutions, but a complete central review of computed tomography or magnetic resonance scans has not been performed yet. There have been no secondary neoplasms so far.

**DISCUSSION**

In most trials of newly discovered childhood ALL, replacement of cRT by IT therapy and/or increased-dose systemic MTX has not been applied to high-risk patients. Relapse may be viewed as definite proof of aggressive leukemic disease, but in several salvage therapy protocols, cRT has been withheld from children with isolated BM relapse for concern about toxicity. The retrospective analysis of the ALL-REZ BFM 85M/87 data suggests that preventive CNS treatment with cRT and prolonged triple IT in children with late isolated BM relapse of ALL reduces the risk of second CNS relapse and improves overall DFS. Increased-dose systemic MTX (1 g/m² over 36 hours) together with IT MTX, administered 8 times during 6 months of intensive polychemotherapy, and use of systemic dexamethasone do not appear to afford CNS protection.

The observations presented here are not based on a randomized prospective trial but on a comparison of two consecutive groups of children who received identical systemic polychemotherapy. Therefore, the conclusions have to be viewed cautiously. Fewer children who received cRT during salvage therapy had received cRT during front-line therapy than children who were not irradiated for relapse treatment. No skewed distribution of parameters known to be associated with a poor prognosis at the time of first or relapse diagnosis was noted for the two consecutive groups. Although completely withholding effective secondary CNS prophylaxis from children in one arm of a randomized prospective trial is viewed as being precluded on ethical grounds (no such trial has ever been conducted in childhood ALL relapse).
the combined approach of cRT and triple IT therapy poses
questions to be answered by randomized trials.

A comparison of 11 non-cRT children who received addi-
tional triple IT therapy during the first half-year of mainte-
nance therapy with 22 non-cRT non-triple IT children
did not show any benefit of this measure. However, it is well
conceivable that continuation of triple IT therapy for a total
of 2 or 3 years might afford CNS protection similar to that
observed with cRT, as shown in front-line protocols. 13 In
a series of 14 standard-risk ALL children with late isolated
BM relapse, no meningeal relapse was observed after pe-
riodic IT MTX and cytarabine was administered for 30
months. 5 Seven children were reported to be in second CR
for at least 48 to 79 months, whereas none of the patients
in the historical control group remained in CR after 2.5 years.
However, children with a late isolated BM relapse of ALL
treated with prolonged triple IT therapy without cRT are
now being reported to have CNS involvement in more than
10% of second relapses observed. 7 Conclusions regarding
the relative contribution of therapy elements to improved
outcome of relapsed ALL patients may not be easily trans-
ferred between study populations differing grossly in front-
line treatment strategy and median duration of first CR.

Although acute and chronic neurotoxicity is inherent to
all available modalities of CNS prophylaxis, cRT has the
additional burden of inducing brain tumors within 1 or 2
decades after radiotherapy. 13-16 Until now, no second mal-
gnancy was observed in the children of this study, but the
possibility of radiation-induced CNS neoplasms developing
later cannot be excluded. In a retrospective cohort study of
9,720 children with ALL, the estimated risks of a second
neoplasm among non-irradiated and irradiated patients were
0.3% and 1.6%, respectively, 10 years after diagnosis. 16 Tu-
mors of the CNS accounted for the majority of neoplasms
in irradiated patients. This has to be weighed against the
gain in survival rate achieved by cRT and triple IT therapy.

Acute neurotoxicity was acceptable both in irradiated and
not irradiated patients. Although a central review of brain
computed tomography scans is currently underway, long-
term follow-up including subtle impairment of intellectual
and endocrinologic functions 17 has not been part of the ALL-
REZ BFM multicenter trials so far. The increased chances of
prolonged survival in patients with late isolated BM relapse
emphasize the need for a comprehensive assessment of long-
term sequelae of potentiately curative treatment strategies.

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REFERENCES

1. Komp DM, Fernandez CH, Falletta JM, Ragab AH, Humphrey
GB, Pullen J, Moon T, Shuster J: CNS prophylaxis in acute lymph-
morphic leukemia. Comparison of two methods. A Southwest Oncol-

2. Sullivan MP, Chen T, Dyment PG, Hvizdale E, Steuber CP:
Equivalence of intrathecal chemotherapy and radiotherapy as central
nervous system prophylaxis in children with acute lymphatic leuko-
emia: A Pediatric Oncology Group study. Blood 60:948, 1982

J: Effective prevention of central nervous system leukemia with intrathecal methotrexate and intrathecal methotrexate, cytosine ara-
obinose, and hydrocortisone in childhood acute lymphocytic leuko-

H: Central nervous system relapse prevention in 1165 standard-
risk children with acute lymphoblastic leukemia in five BFM trials.
Haematol Blood Transfus 33:500, 1990

5. Rivera G, George SL, Bowman WP, Kalwinsky D, Ochs J,
Dahl GV, Hustu HO, Simone J: Second central nervous system
prophylaxis in children with acute lymphoblastic leukemia who re-

6. Pui CH, Bowman WP, Ochs J, Dodge RK, Rivera GK: Cyclic
combination therapy for acute lymphoblastic leukemia recurring

7. Sadowizt PD, Smith SD, Shuster J, Wharam MD, Buchanan
GR, Rivera GK: Treatment of late bone marrow relapse in children
with acute lymphoblastic leukemia: A Pediatric Oncology Group

G, Riehm H: BFM Group treatment results in relapsed childhood
acute lymphoblastic leukemia. Haematol Blood Transfus 33:619,
1990

G, Niethammer D, Riehm H: Six-year experience with a comprehen-
sive approach to the treatment of recurrent childhood acute lymphob-
lastic leukemia (ALL-REZ BFM 85). A relapse study of the BFM

Gerein V, Göbel U, Reiter A, Ritter J, Henze G: Superior prognosis
in combined compared to isolated bone marrow relapses in salvage
therapy of childhood acute lymphoblastic leukemia. Med Pediatr
Oncol 21:470, 1993

Henze G: Risk of CNS relapse after systemic relapse of childhood

12. Jones B, Freeman AI, Shuster JJ, Jaccquilla C, Weil M, Poch-
eddy C, Sinkis L, Chevalier L, Maurer HM, Koch K, Falkson G,
Patterson R, Seligman B, Sartorius J, Kung F, Haurani F, Stuart M,
Burgert O, Ruymann F, Sawitsky A, Forman E, Fluess H, Truman
J, Hakani N, Oldwell O, Glicksman AS, Holland JF: Lower inci-
dence of meningeal leukemia when prednisone is replaced by dexam-
ethasone in the treatment of acute lymphocytic leukemia. Med

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