Improved treatment for acute lymphoblastic leukemia (ALL) has virtually eliminated testicular relapse. However, the control of central nervous system (CNS) leukemia remains a therapeutic challenge in childhood ALL, partly because of the late complications arising from cranial irradiation. In most current pediatric protocols, cranial irradiation (12 to 18 Gy) is given to 5% to 25% of patients—those with T-cell ALL, overt CNS disease (CNS3 status) or high-risk cytogenetics. CNS control is a less urgent concern in adults with ALL, in whom systemic relapse remains the major problem. With current approaches, approximately 2% to 10% of patients can be expected to develop CNS relapse. Children with B-cell precursor ALL who have a late CNS relapse (after an initial remission of 18 months or more) and did not receive cranial irradiation have an excellent outcome after retrieval therapy, with a 5-year event-free survival (EFS) rate approaching that in newly diagnosed patients. Innovative treatment options are needed for children who develop CNS relapses after a short initial remission or after receiving cranial irradiation, and in any adults with CNS leukemia at diagnosis or relapse.

Testicular and other extramedullary relapses have become exceedingly rare in contemporary clinical trials as event-free survival rates have risen to 80% and higher. Yet central nervous system (CNS) relapse remains a major obstacle to cure, accounting for 30% to 40% of initial relapses in some clinical trials. Inadequate control of CNS leukemia is partly related to the decreased use of cranial irradiation for subclinical disease to avoid the long-term sequelae of this treatment modality. Indeed, even in patients with CNS leukemia at diagnosis or relapse, attempts have been made to reduce the dose of therapeutic cranial irradiation. Thus, most contemporary protocols do not specify cranial irradiation for infants or very young children, even if they present with CNS leukemia. Because systemic control of ALL is still problematic in adult patients, less attention has been paid to CNS leukemia in this age group. Reviewed here are examples of the current strategies being taken to optimize CNS-directed therapy in ALL.

Risk Factors for CNS Relapse

Precise assessment of the CNS relapse hazard is critical to avoid over- or undertreatment of patients. Presenting features associated with an increased risk of CNS relapse in pediatric patients include a T-cell immunophenotype, hyperleukocytosis, high-risk genetic abnormalities such as the Philadelphia chromosome and t(4;11), and the presence of leukemic cells in cerebrospinal fluid (even from iatrogenic introduction due to a traumatic lumbar puncture). More recently, polymorphisms in genes that code for proteins involved in the pharmacodynamics of antileukemic drugs have been associated with the risk of CNS relapse. In one study, gene polymorphisms associated with increased CNS relapse include the vitamin D receptor locus (start site and intron 8), presumably by regulating the expression of cytochrome P450 3A4 and P-glycoprotein, and the high-activity thymidylate synthetase 3/3 genotype, which might lead to methotrexate resistance.

It is well recognized that the impact of many prognostic factors can be lessened or eliminated altogether with intensified treatment. For example, CNS2 status (the presence of leukemic cells in a cerebrospinal fluid sample that contains fewer than 5 WBCs/µL) was associated with an increased risk of CNS relapse in many but not all clinical trials (Table 1), apparently because of differences in the efficacy of systemic and CNS-directed therapy among the study groups. Likewise, the increased risk of CNS relapse and poor event-free survival associated with traumatic lumbar puncture with blasts in cerebrospinal fluid can be overcome by more effective therapy (Table 2). This relationship notwithstanding, we contend that identification of a CNS2 status or traumatic lumbar puncture with blasts warrants intensification of therapy to reduce the risk of CNS relapse in these patients. Patients with T-cell ALL and

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Cranial irradiation

Cranial irradiation is a very effective form of CNS-directed therapy, but its efficacy is offset by substantial rates of secondary neoplasms, endocrinopathy, neurocognitive dysfunction, and neurotoxicity.21 Hence, most contemporary pediatric protocols limit the use of this treatment modality to the estimated 5% to 25% of patients who are at particularly high risk for CNS relapse. Investigators of the Berlin-Frankfurt-Münster group showed that among high-risk patients without a CNS3 status (a nontraumatic cerebrospinal fluid sample that contains ≥5 WBC/µL with identifiable blasts, or the presence of a cerebral mass or cranial palsy), the radiation dose can be lowered to 12 Gy without increasing the risk of CNS relapse, provided that effective systemic chemotherapy is used. A randomized trial showed that hyperfractionated (twice daily) cranial irradiation failed to reduce neurocognitive late effects and might have compromised antileukemic efficacy, as compared to conventionally dosed radiation.23

Two pediatric and at least two adult trials have tested the feasibility of omitting cranial irradiation in all patients.22 24 In the pediatric trials, the cumulative risks of isolated CNS relapse were 4.2% and 3.0%, and the rates of any CNS relapse (including combined CNS and hematopoietic stem cell transplantation with 13.2 Gy fractionated total-body irradiation in approximately half of the patients, those with CNS leukemia at diagnosis had a significantly higher risk for any type of CNS relapse, isolated or combined (11.9% vs. 5.6%), and a poorer survival rate (29% vs. 38% at 5 years) compared with all other patients.25

CNS-directed Therapy for Newly Diagnosed Patients

Table 2. Treatment outcome according to CNS1 status and traumatic lumbar puncture with blasts (TLP).

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>CNS1</th>
<th>TLP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFM 95 (1995-1999)(^{10})</td>
<td>1605</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>% CNS relapse at 5 yr</td>
<td>3.5</td>
<td>8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>% 5-yr EFS (SE)</td>
<td>80 (1)</td>
<td>73 (4)</td>
<td>0.003</td>
</tr>
<tr>
<td>DCLSG ALL 7 &amp; 8 (1988-1997)(^{14})</td>
<td>304</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>% CNS relapse at 10 yr</td>
<td>4.9</td>
<td>8</td>
<td>0.24</td>
</tr>
<tr>
<td>% 10-yr EFS (SE)</td>
<td>72.6 (2.5)</td>
<td>58 (7.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SJCRH XI &amp; XII (1984-1991)(^{17})</td>
<td>336</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>% CNS relapse at 5 yr</td>
<td>4.3 (1.1)</td>
<td>7.3 (3.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>% 5-yr EFS (SE)</td>
<td>77 (2)</td>
<td>60 (6)</td>
<td>0.026</td>
</tr>
<tr>
<td>SJCRH XIlIb (1994-1998)(^{15})</td>
<td>145</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>% CNS relapse at 5 yr</td>
<td>0.7 (0.7)</td>
<td>0</td>
<td>0.73</td>
</tr>
<tr>
<td>% 5-yr EFS (SE)</td>
<td>80.6 (3.3)</td>
<td>82.4 (8.9)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Abbreviations: BFM, Berlin-Frankfurt-Münster; CNS, central nervous system; EFS, event-free survival; SE, standard error; DCLSG, Dutch Childhood Leukemia Study Group; ALL, acute lymphoblastic lymphoma; SJCRH, St. Jude Children's Research Hospital

Table 1. Cumulative risk of isolated central nervous system (CNS) relapse according to CNS1 or 2 status in selected clinical trials.

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Study Period</th>
<th>Patient Group</th>
<th>% Cumulative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJCRH XI (^{8})</td>
<td>1984-1988</td>
<td>All</td>
<td>4.0</td>
<td>13.0</td>
</tr>
<tr>
<td>POG 8602 (^{9})</td>
<td>1986-1990</td>
<td>B-lineage</td>
<td>5.3</td>
<td>11.6</td>
</tr>
<tr>
<td>BFM 95 (^{10})</td>
<td>1995-1999</td>
<td>All</td>
<td>3.5</td>
<td>10</td>
</tr>
<tr>
<td>CCG 1800/1900 (^{11})</td>
<td>1988-1993</td>
<td>All</td>
<td>3.9</td>
<td>7.7</td>
</tr>
<tr>
<td>EORTC 58881 (^{12})</td>
<td>1989-1998</td>
<td>All</td>
<td>8.1</td>
<td>15.7</td>
</tr>
<tr>
<td>CCG 105 (^{13})</td>
<td>1983-1989</td>
<td>Non-irradiated</td>
<td>6.5</td>
<td>11.8</td>
</tr>
<tr>
<td>CCG 105 (^{13})</td>
<td>1983-1989</td>
<td>Irradiated</td>
<td>6.4</td>
<td>2.3</td>
</tr>
<tr>
<td>DCLSG ALL-7 &amp; 8 (^{14})</td>
<td>1988-1997</td>
<td>All</td>
<td>3.6</td>
<td>5.4</td>
</tr>
<tr>
<td>SJCRH XIIIB (^{15})</td>
<td>1994-1998</td>
<td>All</td>
<td>0.7</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Abbreviations: SJCRH, St. Jude Children's Research Hospital; POG, Pediatric Oncology Group; BFM, Berlin-Frankfurt-Münster; CCG, Children's Cancer Group; EORTC, European Organisation for Research and Treatment of Cancer; DCLSG, Dutch Childhood Leukemia Study Group; NS, not significant

a presenting leukocyte count of more than 100 × 10⁹/L have perhaps the highest risk of CNS relapse. Indeed, inadequate CNS-directed therapy for such patients may not only increase the risk for CNS relapse, but may also lead to a higher rate of hematologic relapse.8

Besides the mature B-cell phenotype,19 only a few factors have been associated with an increased risk for CNS relapse in adults with ALL. In a recent study, Lazarus et al20 reported that a T-cell phenotype, high presenting leukocyte counts and the presence of a mediastinal mass were associated with CNS leukemia at diagnosis. Despite intensified chemotherapy and craniospinal irradiation (24 Gy cranial and 12 Gy spinal), or hematopoietic stem cell transplantation with 13.2 Gy fractionated total-body irradiation in approximately half of the patients, those with CNS leukemia at diagnosis had a significantly higher risk for any type of CNS relapse, isolated or combined (11.9% vs. 5.6%), and a poorer survival rate (29% vs. 38% at 5 years) compared with all other patients.25

We contend that early intensive systemic and intrathecal chemotherapy could reduce the CNS relapse hazard to a negligible level, permitting the omission of cranial irradiation with all other patients.20
irradiation in all patients, and are conducting a clinical trial to test this hypothesis. By the same token, it seems reasonable to predict a very high remission retrieval rate for pediatric patients with an isolated CNS relapse who have not received cranial irradiation as initial CNS-directed therapy. Indeed, children with B-cell precursor ALL and a long initial remission before CNS relapse have a long-term therapy. Thus, one may be able to reserve cranial irradiation for salvage therapy, so that most patients would be spared its toxic effects.

Intrathecal therapy

In an early study, investigators of the Pediatric Oncology Group showed that triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine could yield results comparable to those achieved with cranial irradiation, and that intrathecal therapy could be reduced from 3 years to 1 year in patients with good-risk leukemia. Recently, however, a randomized study was performed to compare the efficacy of triple intrathecal therapy with that of intrathecal methotrexate only. In that trial, triple intrathecal therapy reduced the frequency of isolated CNS relapse but unexpectedly was associated with an increased frequency of bone marrow and testicular relapse, leading to an inferior survival rate overall. One explanation for this seemingly paradoxical finding is that “isolated” CNS relapse is an early manifestation of systemic relapse, and that the better CNS control secured with triple intrathecal therapy versus intrathecal methotrexate favors overt leukemic relapse in other sites. If so, more effective systemic chemotherapy will be needed before the full benefit of triple intrathecal therapy can be realized.

Regardless of the type of intrathecal treatment used, careful attention should be paid to its optimal administration. For example, intrathecal medication given in a large volume (6 mL or more) attains a better distribution within the CNS than does a smaller volume. After the procedure, patients should remain in a prone position for at least 30 minutes, which in a non-human primate model was shown to increase significantly the intraventricular level of medication. Whether the use of a blunt “pencil-point” spinal needle could improve CNS control by preventing leakage of cerebrospinal fluid and intrathecal chemotherapy remains to be studied.

It is also important to prevent traumatic lumbar puncture, especially at diagnosis when the majority of patients have abundant circulating leukemic blasts. Traumatic lumbar puncture has the potential to increase the risk of CNS relapse and result in poor event-free survival. Such procedures adversely affect not only the initial intrathecal injection of therapy but also subsequent treatments because of the collapse of the thecal sac due to hematoma or cerebrospinal fluid collection, or to scarring or segmentation of the subarachnoid membrane. Even though the poor prognostic impact of traumatic lumbar puncture can be abolished by intensive systemic and intrathecal therapy, every effort should be made to prevent its occurrence because intrathecal therapy can also adversely affect neuropsychologic and spinal cord functions. Since recognition of the adverse consequences of traumatic lumbar puncture, we correct thrombocytopenia before the diagnostic lumbar puncture, which is followed immediately by intrathecal treatment. Finally, intrathecal therapy is routinely performed by the most experienced clinician in our center, with patients under deep sedation or general anesthesia.

Systemic chemotherapy

It is well recognized that systemic chemotherapy can influence the control of extramedullary leukemia. In a meta-analysis of 43 randomized trials, high-dose methotrexate reduced the hematologic relapse rate and improved event-free survival, but had only a marginal effect on the control of CNS leukemia. This outcome may reflect the generally lower dose of methotrexate (0.5 to 1 g/m²) used in the past, suggesting that higher doses (e.g., 5 g/m² as in many current trials) would be more effective in securing CNS control.

In two recent randomized trials, patients treated with dexamethasone at a daily dosage of 6 to 6.5 mg/m² had lower rates of CNS relapse and better event-free survival rates than those treated with prednisone at 40 mg/m². This finding was attributed to increased penetration of dexamethasone into the CNS due to its low protein-binding property and its longer half-life. However, a recent randomized study showed comparable results when patients were randomized to receive dexamethasone at 8 mg/m² per day and prednisolone at 60 mg/m² per day, a finding suggesting that previous clinical trials might not have used equivalent doses of the two drugs. It is well recognized that systemic chemotherapy can influence the control of CNS leukemia.

Treatment of CNS Relapse

Depending on the efficacy of systemic chemotherapy and on the proportion of patients treated initially with cranial irradiation, approximately 2% to 10% of patients with ALL will develop isolated CNS relapse (Table 1). The strategy of delaying cranial or craniospinal irradiation for 6 to 12 months to allow initial intensification of systemic chemotherapy has yielded long-term second event-free survival rates of 70% to 80% in children with isolated CNS relapse. These excellent results led investigators in the Children’s Oncology Group to reduce the radiation dose in a subsequent study. Patients with an initial remission duration of < 18 months received 24 Gy cranial and 15 Gy spinal irradiation, while those with a longer initial remission received only 18 Gy cranial irradiation at 12 months of treatment. Despite the reduction of radiation dose, pa-
tients whose initial remission persisted for > 18 months have an excellent 4-year event-free survival rate of 77.7%.27 It should be noted that this result applies only to children with B-lineage ALL who did not receive cranial irradiation during initial treatment. Interestingly, besides a long initial remission, a standard-risk status at diagnosis by NCI/Rome criteria (i.e., age 1 to 9.9 years with leukocyte count < 50 × 10⁹/L) was an independent favorable prognostic factor in the study. Nonetheless, CNS relapse in pediatric patients with a short initial remission duration, T-cell ALL, or prior cranial irradiation continues to pose a therapeutic challenge.

Very few studies have addressed isolated CNS relapses in adults with ALL. Of 22 adults who developed isolated CNS relapse in the MRC UKALL12/ECOG2993 study, only 3 were alive at the time of the report with an estimated overall 5-year survival rate of zero.29 In another study of patients treated in M.D. Anderson Cancer Center between 1982 and 2000, 17 isolated CNS relapses were identified among 527 consecutive patients who did not receive cranial irradiation for prophylaxis.40 The outcome for this group of patients was also dismal: 15 patients developed a subsequent hematologic relapse and 1 died in remission after 3 years; only 1 patient was alive and free of leukemia after 5 years. Since only 5 of these 17 patients received reinduction chemotherapy at the time of CNS relapse,40 more intensive retrieval therapy might improve the future outlook for adults with isolated CNS relapse.

**Future Directions**

More effective chemotherapy is needed for patients who have had a CNS relapse or have a very high risk of developing this complication. Treatment strategies that could improve outcome in these subgroups include frequent and early intrathecal therapy as used for Burkitt leukemia/lymphoma; intrathecal liposomal cytarabine, which can maintain a therapeutic level of cytarabine in cerebrospinal fluid for 2 weeks or more;41 and intraventricular administration (more preferable for adults). Ongoing studies are testing whether the dose of cranial irradiation can be further reduced in patients with isolated CNS relapse and long initial remissions. To this end, in the Rotterdam-84 CNS-ALL chemotherapy protocol, intensive systemic and intraventricular therapy (methotrexate 6 mg on days 1 and 3, and cytarabine 60 mg on day 2) without the use of CNS radiotherapy yielded a 5-year event-free survival rate of 59 ± 14% (SE) among 13 children with isolated CNS relapse who had no prior irradiation (Beishuizen A and Hählenk K, presented in the 5th Bi-annual Symposium on Childhood Leukemia, Noordwijkerhout, the Netherlands).

**References**


