TRIPLE INTRATHECAL THERAPY ALONE WITH OMISSION OF CRANIAL RADIATION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Purpose
To eliminate the toxicities and sequelae of cranial irradiation (CrRT) and to minimize the adverse impact of traumatic lumbar puncture (TLP) with blasts, a prospective study of a modified CNS-directed therapy was conducted in children with acute lymphoblastic leukemia (ALL).

Patients and Methods
Since June 1999, children with newly diagnosed ALL have been treated with triple intrathecal therapy (TIT) alone without CrRT. The first TIT was delayed until the disappearance of blasts from peripheral blood (PB) for up to 10 days of multidrug induction, and CrRT was omitted in all patients. If PB blasts persisted on treatment day 10 (d10), the TIT was then performed.

Results
Of a total of 156 patients, 152 were eligible. Seventeen patients did not have PB blasts at diagnosis. Three fourths of the remaining patients achieved complete clearance of PB blasts by d10. Only hyperleukocytosis at diagnosis showed a significantly lower clearance rate. Six standard-risk patients were upgraded to high risk because of detectable PB blasts on d10. TLPs were encountered in four patients (2.6%), but none were contaminated with lymphoblasts. Neither CNS-2 (less than 5 WBCs/μL with blasts in a nontraumatic sample) nor CNS-3 (5 WBCs/μL with blasts in a nontraumatic sample or the presence of cranial nerve palsy) was present. The 5-year event-free survival and overall survival rates were 84.2% and 90.6%, respectively. No isolated CNS relapse occurred, but two patients experienced combined CNS relapses. The 7-year cumulative risk of any CNS relapse was 1.4%.

Conclusion
Delaying first TIT until circulating blasts have cleared may improve CNS control in children with newly diagnosed ALL and preclude the need for CrRT.

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INTRODUCTION

The importance of CNS-directed therapy for childhood acute lymphoblastic leukemia (ALL) was first highlighted by investigators at St Jude Children Research Hospital (St Jude) in the mid-1960s. They showed that combined therapy of cranial irradiation (CrRT) and intrathecal methotrexate (MTX) can reduce CNS relapse. Together with effective systemic chemotherapy, triple intrathecal therapy (TIT) with MTX, hydrocortisone, and cytarabine yields results comparable to those produced by CrRT. The substantial rates for CrRT-associated complications, including second cancers, cognitive deficits, and endocrinopathy, are well recognized, and most contemporary ALL treatment protocols aim to limit the use of CrRT. The early intensification of TIT was shown to decrease CNS relapse and boost the event-free survival (EFS) rate. Further, Pui et al demonstrated that with effective risk-adjusted systemic chemotherapy and intrathecal therapy initiated at diagnosis, CrRT can safely be omitted from CNS-directed treatment without compromising overall survival (OS) results in all newly diagnosed ALL.

The presence of blasts in the cerebrospinal fluid (CSF) was reported to be a prognostic factor predictive of CNS relapse. Manabe et al specified that lumbar puncture (LP) and TIT should be delayed until after the prephase of 1 week of prednisolone monotherapy instead of using both prednisolone and intrathecal MTX at the time of diagnosis, as the original Berlin-Frankfurt-Münster group did. Furthermore, the iatrogenic introduction of
circulating blasts into CSF by a traumatic lumbar puncture (TLP) at the time of diagnosis resulted in adverse effects for the treatment outcome. The modifiable risk factors for TLP included platelet counts at initiation and the experience of practitioners. The occurrence of TLP needs to be kept to a minimum, but it is actually unavoidable.

With the intent of eliminating CrRT-related complications and minimizing the adverse prognostic impact of TLP with blasts, we conducted a prospective study beginning in 1999 to modify CNS-directed therapy for patients with newly diagnosed ALL. In this study, the first TIT was delayed until the disappearance of blasts from peripheral blood (PB) for up to 10 days of multidrug induction, and CrRT was omitted for all risk groups. Here we report the long-term treatment outcomes of this study.

**PATIENTS AND METHODS**

**Patients**

This study enrolled all children with newly diagnosed ALL at our hospital from June 1999 to August 2010. The diagnosis of ALL was based on immunophenotyping and on morphologic, cytochemical, cytogenetic, and molecular analysis of leukemic cells. These patients were treated with two successive protocols from the Taiwan Pediatric Oncology Group (TPOG): TPOG-ALL-97 (1997-2001) and TPOG-ALL-2002 (2002-2012). At our hospital, CNS-directed therapy was modified to include TIT alone with delay of first TIT and omission of CrRT in all patients. All protocols were approved by the institutional review board of our hospital. Written informed consent was obtained for all patients.

**Treatment**

Patients with B-precursor ALL were further stratified into standard-risk (SR), high-risk (HR), and very-high-risk (VHR) groups, according to age, WBC count, cytogenetics, and molecular analysis at diagnosis. The SR group was defined as follows: WBC less than $10 \times 10^9$/L for patients age 1 to 2 years and 7 to 10 years, and WBC less than $50 \times 10^9$/L for those age 2 to 7 years. The VHR group included patients with one of the following criteria: WBC more than $100 \times 10^9$/L; T-cell ALL, age younger than 1 year; t(9;22)/BCR-ABL, t(4;11)/MLL-AF4, other MLL gene rearrangements, hypodiploidy (chromosomes < 44), testicular leukemia at diagnosis, and SR or HR patients with poor treatment response. Poor treatment response was defined as not achieving complete remission at the end of induction. The remaining patients and those patients with CNS leukemia (CSF ≥ 5 WBCs/μL with blasts), cranial nerve palsy, or t(1;19)/E2A-PBX1 were classified as being in the HR group.

Treatment components of TPOG-ALL-97 and TPOG-ALL-2002 protocols have been previously reported and are listed in the Data Supplement. The first TIT was performed after the disappearance of blasts from PB. However, if PB blasts were persistent on treatment day 10 (d10), when there are usually ≤ 2% blasts present, TIT was performed as soon as possible. Furthermore, in SR patients with detectable blasts on d10, the treatment protocol was upgraded to that for the HR group. Exceptions were made for patients who presented with cranial nerve palsy or other evidence of CNS disease; LP and first TIT were initiated on the day of diagnosis. CrRT was totally omitted in all patients. The CNS status was defined as follows: CNS-1, no blasts in a nontraumatic sample; CNS-2, less than 5 WBCs/μL with blasts in a nontraumatic sample; CNS-3, ≥ 5 WBCs/μL with blasts in a nontraumatic sample or the presence of cranial nerve palsy. For patients with CNS-1 status, the SR group received TIT 20 times in the TPOG-ALL-97 protocol and 14 times in the TPOG-ALL-2002 protocol. HR patients with CNS-1 status received TIT 23 in the TPOG-ALL-97 protocol and 17 times in the TPOG-ALL-2002 protocol. In the VHR group, TIT was administered 19 times for CNS-1. Patients with CNS-2, CNS-3, and TLP with blasts received two additional TIT treatments during induction therapy. The SR group with CNS-2 or TLP with blasts received 19 doses of TIT. The HR groups with CNS-2, CNS-3, or TLP with blasts received 25 doses of TIT. If VHR patients had CNS leukemia at diagnosis, TIT was administered once per week until achieving CSF remission and then once every 4 weeks during continuation therapy. All TIT procedures were performed by one of our most experienced clinicians and by using short-acting anesthesia. For the first administration of TIT, the platelet count was kept at ≥ $100 \times 10^9$/L if transfusion was needed. The dosages of TIT were age-dependent (Data Supplement).

**Statistical Analysis**

The duration of EFS was measured from the date of patient enrollment to the date of first treatment failure (induction failure, relapse, death, or the development of a second malignancy) or, if no such event occurred, until the last follow-up date. Patients who did not achieve a complete remission were assigned an EFS of zero. EFS and OS rates were estimated by the Kaplan-Meier method and were compared by using the log-rank test.

For patients who achieved complete remission, cumulative incidence functions of isolated CNS or any CNS relapse were estimated by the method of Kalbﬂeisch and Prentice. An isolated CNS relapse was defined as one without simultaneous relapse at another site, and any CNS relapse was defined as a relapse in the CNS accompanied by relapse in the bone marrow (BM) or any other extramedullary site. Differences in the distribution of individual factors among patient subgroups were analyzed by using the χ² test or Fisher’s exact test. Yates’ correction was used if appropriate. The database used for analyses was last updated on October 31, 2012.

**RESULTS**

From June 1999 to August 2010, a total of 158 children with ALL were consecutively diagnosed at our hospital. There were 86 patients in the SR group, 41 in the HR group, and 31 in the VHR groups. Six patients were excluded: two refused further treatment and four had protocol violations. One hundred fifty-two patients, including 86 boys and 66 girls, were eligible for the study. The median age at diagnosis was 4.1 years (range, 0.3 to 17.7 years), and seven patients were infants. The median WBC count at diagnosis was 12.1 $\times 10^9$/L (range, 0.8 to 596 $\times 10^9$/L); 14 patients had WBC counts greater than $100 \times 10^9$/L. There were 141 patients with B-precursor ALL and 11 with T-cell ALL. Table 1 summarizes the clinical characteristics of patients. At diagnosis, none of the study cohort presented with cranial nerve palsy or other evidence of CNS disease. Seventeen patients (11.2%), including 16 SR and one VHR, did not have detectable blasts in PB. After 10-day induction therapy that included prednisolone, vincristine, epirubicin (for SR and HR)/idarubicin (for VHR), and/or l-asparaginase, blasts were eliminated from PB in another 101 patients, resulting in a total of 77.6% of patients without blasts on d10. The clearance rates were 82.1% for SR, 75.6% for HR, and 66.7% for VHR patients ($P = .22$). Only patients with higher WBC counts (> $100 \times 10^9$/L) showed significantly lower clearance rate ($P = .02$; Table 1). Six patients in the SR group were upgraded to the HR protocol because of the persistent detection of PB blasts on d10. TLP was apparent in four patients (2.6%), but no lymphoblasts were identified in the CSF of any patients. Neither CNS-2 nor CNS-3 was present in our patients.

In total, 17 patients relapsed and 11 did not respond to salvage therapy. One boy with high-risk B-precursor ALL experienced BM relapse 12.5 years after diagnosis. Interestingly, he developed a new BCR-ABL transcript which was not detected at the original diagnosis.
He died of sepsis before administration of dasatinib. The follow-up duration of 133 surviving patients ranged from 2.3 to 13 years (median, 7.6 years). The 5-year EFS and OS rates ± SE were 84.2% ± 3.0% and 90.6% ± 2.4%, respectively (Fig 1). The survival outcomes did not differ between patients with or without detectable blasts on d10 (P = .44 for EFS and P = .32 for OS). No isolated CNS relapse occurred. Combined CNS relapses were documented in two patients. Neither of them had TLP in their first TIT. One infant with a WBC count of 215 × 10⁹/L and t(11;19)/MLL-ENL who had detectable blasts on d10 developed combined CNS, BM, and testicular relapses 2.3 years after diagnosis. He died of refractory disease. The other combined CNS and BM molecular relapses occurred in a boy 2.5 years after diagnosis. The patient had t(12;21)/ETV6-RUNXI and did not have blasts on d10. He received salvage therapy that included CrRT and was disease free for 1.3 years after relapse. For 148 patients who achieved complete remission, the 7-year cumulative risk of any CNS relapse was 1.4% ± 1.0% (Fig 1).

### Table 1. Clinical Characteristics of Patients According to the Clearance of PB Blasts on Treatment Day 10

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients Without PB Blasts on Day 10</th>
<th>No. of Patients With PB Blasts on Day 10</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years</td>
<td>1-9</td>
<td>121</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>≥ 10</td>
<td>24</td>
<td>19</td>
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<tr>
<td>Sex</td>
<td>Male</td>
<td>86</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>66</td>
<td>52</td>
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<tr>
<td>WBC × 10⁹/L</td>
<td>≤ 100</td>
<td>138</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>&gt; 100</td>
<td>14</td>
<td>7</td>
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<tr>
<td>Risk group</td>
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<td>69</td>
</tr>
<tr>
<td></td>
<td>High</td>
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<tr>
<td></td>
<td>Very high</td>
<td>27</td>
<td>18</td>
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<tr>
<td>t(9;22)/BCR-ABL</td>
<td>Present</td>
<td>135</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>133</td>
<td>101</td>
</tr>
<tr>
<td>t(1;19)/E2A-PBX1</td>
<td>Present</td>
<td>135†</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>129</td>
<td>97</td>
</tr>
<tr>
<td>t(12;21)/ETV6-RUNXI</td>
<td>Present</td>
<td>135†</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>129</td>
<td>100</td>
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<td>MLL rearrangement</td>
<td>Present</td>
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<td>100</td>
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<tr>
<td>Modal No. 51-88†</td>
<td>Present</td>
<td>135†</td>
<td>105</td>
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</table>

Abbreviation: PB, peripheral blood.

†Chromosome number.
relapses. Furthermore, a recent randomized trial for SR patients, Children’s Cancer Group-1952 (CCG-1952; Combination Chemotherapy in Treating Children With Newly Diagnosed Acute Lymphoblastic Leukemia), showed that TIT significantly reduced isolated CNS relapse compared with intrathecal MTX but was associated with increased BM and testicular relapses, resulting in a worse OS rate. The paradoxical finding also suggests that effective systemic therapy is needed to realize the full benefit of TIT. In this study, we demonstrated that delaying the first TIT until after PB blasts have disappeared with multidrug induction therapy can effectively prevent CNS relapse in children with ALL. Our approach achieved complete clearance of PB blasts in 77.6% of all patients on d10 of induction and reduced the adverse impacts of TLP without compromising treatment outcomes. The incidence of TLP was minimized to 2.6%, and no LPs were contaminated with blasts. No CNS-2 nor CNS-3 status occurred in the first LP, and no isolated CNS relapse occurred. The cumulative incidence of any CNS relapse was only 1.4% ± 1.0% at 7 years. The 5-year EFS and OS rates were 84.2% ± 3.0% and 90.6% ± 2.4%, respectively. CrRT was completely omitted for CNS prophylaxis in our treatment protocols, thus eliminating the complications and sequelae of CrRT.

The St Jude group first proposed a classification of CNS status on the basis of CSF findings: CNS-2 and CNS-3 comprised 12% and 5%, respectively, of first LP performed at the time of diagnosis. In a review article, the reported rates varied from 5.4% to 32.2% for CNS-2 and from 2.1% to 4.7% for CNS-3. Regarding the study design, one may question whether delayed first TIT may underestimate the actual incidences of CNS-2 and CNS-3 status at diagnosis and thus under-treat the patients who need more TIT. For those who presented with blasts in peripheral blood at diagnosis (83% in this study), we gave induction therapy, which included medications effective for CNS disease for, at most, 10 days to lower the CNS status to CNS-1. Therefore, all of the patients we treated had CNS-1 status.

Our simple approach can be used in developing countries to improve outcome. However, this study has some limitations that need to be mentioned. First, this was a single-institution study with a relatively small number of patients. It should be considered a pilot study, and the results need to be confirmed by other groups. Second, the number of patients with T-cell ALL is rather small (7.2%), but the low percentage is typical for Chinese patients in Taiwan (approximately 10%). Moreover, there were no patients with clinically overt CNS disease at diagnosis, so we cannot assess efficacy in that subgroup.

In conclusion, delaying first TIT until after the clearance of circulating blasts may decrease CNS relapse in children with newly diagnosed ALL. This approach using effective chemotherapy and successful TIT may preclude the need for CrRT in CNS prophylaxis regimens.

REFERENCES


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Der-Cherng Liang
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Provision of study materials or patients: Hsi-Che Liu, Ting-Chi Yeh, Der-Cherng Liang
Collection and assembly of data: All authors
Data analysis and interpretation: Hsi-Che Liu, Der-Cherng Liang
Manuscript writing: All authors
Final approval of manuscript: All authors


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