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Treatment of Young Children With CNS-Positive Acute Lymphoblastic Leukemia Without Cranial Radiotherapy

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Background. Due to the long-term sequelae of cranial radiotherapy (CRT), contemporary treatment protocols for children with acute lymphoblastic leukemia (ALL) aim to limit the use of prophylactic CRT. For patients with central nervous system (CNS) involvement with ALL at diagnosis, the use of CRT remains common. Children <5 years of age are a particularly challenging subgroup in whom the consequences of CRT can be devastating. ***Procedure.*** This study retrospectively describes the overall (OS) and event-free survival (EFS) of young children (1–5 years) who were treated for CNS-positive ALL at the Hospital for Sick Children between 2000 and 2013. ***Results.*** Of a total of 19 patients, two were treated with upfront CRT, both as part of the conditioning regimen prior to HSCT. All patients received intensification of CNS-directed chemotherapy by triple intrathecal chemotherapy (84.2%), use of dexamethasone in induction (57.9%) and maintenance (66.7%), and high-dose methotrexate (77.8%). The OS was 84.28.4% and EFS was 79.09.4% with a median follow-up time of 4.3 years (range, 2.6–8.2). The cumulative incidence of CNS relapse was 5.25.1%. ***Conclusions.*** We conclude that omission of CRT from the treatment of young children with ALL involving the CNS is associated with acceptable survival and avoids potentially devastating late effects in this group. Pediatr Blood Cancer 2015;62:1881–1885. © 2015 Wiley Periodicals, Inc.

Key words: acute lymphoblastic leukemia (ALL); long-term survival; pediatric oncology; radiation therapy

INTRODUCTION

Intensified multi-agent chemotherapy has improved the 5-year survival of children with acute lymphoblastic leukemia (ALL) to just over 90%.[1] The presence of leukemia in the central nervous system (CNS) at diagnosis, however, is associated with inferior outcome compared to patients without CNS involvement.[2–4] Current trials have replaced prophylactic cranial radiotherapy (CRT) with systemic and intrathecal therapy (IT) in the majority, and in some cases all ALL patients without overt CNS disease in order to prevent late effects associated with CRT such as neurocognitive deficits, endocrinopathies and secondary brain tumors.[5–7] Nearly all large cooperative groups continue to use CRT for CNS leukemia at diagnosis. Two recent studies have omitted CRT from the treatment of children with precursor B-ALL including those with CNS involvement (CNS-3). The St. Jude total therapy XV study omitted both prophylactic and treatment CRT and reported a 5-year event-free survival (EFS) of 85.6%, an overall survival (OS) of 93.5%, and isolated CNS relapse rate of <3%. However, this study included only nine CNS-3 patients who had a 5-year EFS of 43.2%.[8] Similarly, the Dutch childhood oncology group (DCOG) ALL-9 study omitted CRT in all their ALL patients, and included 21 CNS-3 patients who had a 5-year EFS of 67%.[9] The outcome of CNS-3 patients treated without CRT in the context of other chemotherapy backbones is unknown.

Given the inverse relationship between severity of adverse neurocognitive and endocrine effects of cranial irradiation and patient age,[10] over time, our institution adopted the approach of omitting CRT for patients younger than 5 years of age even in the presence of CNS involvement at diagnosis. Instead CNS-directed therapy was augmented in this group through intensified intrathecal and systemic chemotherapy. The objective of this study is to report the survival outcomes associated with this approach.

METHODS

Ethical approval was obtained from the Institutional Review Board of the Hospital for Sick Children, Toronto. Due to the nature of the study and number of charts reviewed, requirement for informed patient consent was waived by the IRB. A retrospective chart review of all patients between 1 and 5 years of age who were diagnosed with ALL between January 1, 2000 and May 31, 2013 was conducted. This time period was selected because it followed the introduction at our institution of treatment for ALL involving the CNS in children under the age of 5 years without CRT in the majority of patients. The decision to omit CRT was not taken in the context of a research study, but rather after a discussion with parents of the anticipated risks and benefits of omitting versus proceeding with CRT in young children. In general, the parents or legal guardians were informed i) that CRT was the standard treatment for ALL involving the CNS even in young children at most centers ii) that a significant concern regarding irreversible neurocognitive effects of CRT had led our center to use an alternative approach consisting of intensified systemic and intrathecal chemotherapy without CRT in children under the age of 5 years iii) that this alternative approach was expected to avoid the neurocognitive late effects of CRT in young children but could result in a higher risk of leukemic relapse in the CNS iv) that there were potential adverse effects of substituting single intrathecal MTX with triple intrathecal chemotherapy and prednisone with dexamethasone. If after this discussion parents concluded that the potentially higher risk of relapse after treatment without CRT was outweighed by the avoidance of the adverse neurocognitive effects of CRT at a young age, treatment without CRT was used. Otherwise, the treating team was prepared to include CRT in a patient's treatment plan. Only children under 5 years of age who had evidence of CNS leukemia at diagnosis were included in this study. CNS leukemia was defined by positive CSF cytology at the time of diagnosis (5 or more WBC/μl

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Conflict of interest: Nothing to declare

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cerebrospinal fluid and cytospin positive for lymphoblasts, CNS-3; or traumatic puncture positive by Steinherz–Bleyer algorithm) or clinical and/or radiographic evidence of CNS involvement.[11] The type of intensification was initially based on physicians' preference and eventually resulted in the use of dexamethasone as glucocorticoid, high-dose methotrexate, and triple intrathecal chemotherapy as our standard of care for the majority of patients in this group (Table I). Children who were classified as having CNS-2 disease and those with Down syndrome were excluded. Data regarding patient demographics, diagnosis, treatment, early response, relapse, and survival at last follow up were collected.

Statistical Analysis

Statistical analysis was predominantly descriptive. OS was defined as the time from diagnosis to death from any cause. EFS was defined as the time from diagnosis to relapse, progression, second malignancy, or death from any cause. For the primary analysis, patients were censored at the last reported contact if no event had occurred. A secondary analysis also censored patients at the time of hematopoietic stem cell transplantation. OS and EFS were estimated by the Kaplan–Meier method. The cumulative incidence of any relapse involving the CNS was calculated with death, isolated bone marrow relapse, and second malignancies considered competing events. Analyses were performed using SAS for UNIX, version 9.2.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

During the study period, 19/505 (3.7%) children diagnosed with ALL at our center met inclusion criteria (younger than 5 years of age and with CNS leukemia at diagnosis). Patient characteristics are summarized in Table I. The majority (16/19, 84%) of patients had B-precursor ALL; three had T-cell ALL of whom one had Early-T precursor (ETP) ALL. Thirteen (68.4%) patients were NCI Standard Risk based on presenting white blood cell count. Of the 19 patients, eight (42%) had traumatic lumbar punctures and were positive by the Steinherz–Bleyer algorithm. Five patients (26%) were classified as CNS3 based on the presence of neurological symptoms and/or abnormal neuroimaging. Out of 15 patients for whom both cytogenetic and molecular data were available, eight (53%) had identifiable translocations. Two patients had a normal karyotype and the remainder had variable additions of whole chromosomes (Table I).

Treatment

The treatment and follow-up data of all 19 patients are detailed in Table I. Seventeen patients (89.4%) were treated with chemotherapy alone. Two patients underwent hematopoietic stem cell transplant (HSCT) in first remission, one for Philadelphia-positive ALL prior to the current treatment era of tyrosine kinase inhibitor use (Patient 3) and one for ETP-ALL with positive minimal residual disease (MRD) at the end of induction (Patient 19). Both patients were conditioned with cyclophosphamide and total body irradiation (TBI). No other patient received cranial irradiation during primary ALL therapy.

All patients were treated with augmented BFM chemotherapy regimens as per contemporary North American children's oncology group (COG) treatment protocols. Only four patients were initially registered on a COG study but were subsequently taken off due to the decision to omit CRT. Among patients in whom full treatment data were available (and who completed the relevant phase of therapy), 11/19 (57.9%) were treated with dexamethasone in induction. Of the 15 patients who reached maintenance, 10 (66.7%) received dexamethasone during that phase. In total, only one patient was treated with prednisone in both induction and maintenance. Seventeen (100%) patients were treated with an intensified consolidation using cyclophosphamide and cytarabine (one patient died prior to consolidation, one patient had missing data), 14/18 (77.8%) with high-dose methotrexate in interim maintenance, 9/15 (60%) with double delayed intensification, and 16/19 (84.2%) with triple intrathecal therapy (TIT). The median number of single IT injections was six and that of TIT injections was 18, with a median of 24 total ITs.

Outcome

All patients were in morphological remission at the end of induction (day 29). Bone marrow MRD was positive ($>10^{-4}$) in three out of 10 patients for whom data were available. With a median follow-up time of 4.3 years (range, 2.6–8.2), the 5-year OS for the total cohort was 84.2% ($\pm$8.4) and 5-year EFS 79.0% ($\pm$9.4). Kaplan–Meier curves are shown in Figure 1. The cumulative incidence of CNS relapse was 5.2% ($\pm$5.1) at 5 years. Causes of death included septic shock on day 0 of HSCT (Patient 3), diffuse alveolar injury on day 100 post HSCT (Patient 19), and septic shock on day 43 of induction (Patient 7). One patient (Patient 17) experienced a very early isolated CNS relapse on day 1 of interim maintenance. This patient subsequently underwent HSCT and is currently in second remission. Figure 2 illustrates survival analysis for the same cohort with patients censored at the time of HSCT. When censored this way, 5-year EFS for the cohort was 89.5% ($\pm$7.0) and 5-year OS was 94.7% ($\pm$5.1).

Of the total cohort, three patients had ALL with a precursor T immunophenotype, one of whom had ETP. Two patients died. Patient 7 died of ARDS and chemotherapy induced pancytopenia after induction. Patient 19 underwent HSCT in first remission due to high minimal residual disease at the end of induction and died of transplant-related complications.

DISCUSSION

Involvement of the CNS at the time of ALL diagnosis is a widely accepted risk factor for leukemic relapse, and constitutes an indication for cranial irradiation in the majority of contemporary treatment protocols.[2–4] The benefit of cranial irradiation of reducing relapse risk, however, must be weighed against the known late effects of this modality such as neurocognitive impairment, endocrine deficiency and secondary brain tumors.[5–7] This risk-benefit calculation is particularly relevant in young children who are expected to be at greater risk for irreversible neurocognitive deficits.[10] Our institution, therefore, has over time discontinued the routine use of cranial irradiation in young children (under the age of 5 years) with CNS-positive ALL and instead adopted intensification of CNS-directed chemotherapy for this group of patients.

This approach is in line with the few contemporary ALL trials that have tried to completely omit this treatment modality. Although a number of early studies had demonstrated low cumulative risk of

TABLE I. Patient Treatment and Outcome

Patient ID	Immuno-phenotype	WBC ($\times 10^9$/L)	Initial CSF WBC (x10^6/L)	Traumatic LP (Y/N)	Diagnosis month/ year	Age (yrs)/ gender at diagnosis (M/F)	Genetics	Treatment				Cumulative dose of HD-MTX (g/m^2)	D29 MRD %	HSCT	Event[a]	Final status	Month/ year of last follow up
								Steroid[b]	MTX[c]	DI	Intrathecal therapy[d]						
1	Prec B	6.1	7	N	10/2000	1.7F	NH	Pred	Escal.	Double	Triple	n/a	ND	No	None	CR	09/2013
2	Prec B	9.2	2[e]	N	02/2000	2.2F	HD, DT	Pred	HD	Single	Triple	24	ND	No	None	CR	12/2013
3	Prec B	65.2	0[e]	N	12/2000	3.8M	HD, DT t(9;22)	Pred	HD	n/a	Single	24	ND	Yes	TRM	Deceased	07/2001
4	Prec B	5.0	19	N	08/2002	2.9M	NH	Pred	Escal.	Double	Triple	n/a	ND	No	None	CR	11/2013
5	Prec B	1.9	7	N	07/2002	2.2M	HD, DT	Pred	Escal.	Double	Single	n/a	ND	No	None	CR	10/2013
6	T	21.4	7	Y	07/2003	1.6M	NH	Pred	HD	Single	Triple	20	ND	No	None	CR	07/2011
7	T	463.1	16	Y	02/2003	4.7M	ND	Pred	n/a	n/a	Triple	n/a	ND	No	TRM	Deceased	03/2003
8	Prec B	65.6	53	Y	12/2004	1.7M	NH t(9;16) t(9;19)	Dex	HD	Double	Triple	20	ND	No	None	CR	02/2013
9	Prec B	25.2	2[e]	N	10/2006	1.3F	NH t(12;19)	Dex	HD	Double	Triple	20	ND	No	None	CR	08/2013
10	Prec B	13.1	19	Y	06/2007	1.3F	H, DT	Dex	Escal.	Double	Triple	n/a	<0.01	No	None	CR	02/2013
11	Prec B	167.0	58	Y	12/2008	1.3F	NH t(1;19)	Dex	HD	Double	Triple	20	<0.01	No	None	CR	08/2013
12	Prec B	13.8	7	Y	04/2009	1.6F	NH	Dex	HD	Double	Triple	20	0.14	No	None	CR	06/2013
13	Prec B	58.3	7	Y	04/2009	4.6F	NH t(12;21)	Dex	HD	Double	Triple	20	<0.01	No	None	Alive	08/2013
14	Prec B	20.2	0[e]	N	10/2010	3.1M	H, DT	Dex	HD	Single	Triple	20	<0.01	No	None	Alive	11/2013
15	Prec B	19.8	9	N	04/2011	3.9M	H, DT t(10;12)	Dex	HD	Single	Triple	20	<0.01	No	None	Alive	11/2013
16	Prec B	6.3	0[e]	N	06/2011	3.4F	NH t(1;19)	Dex	HD	Single	Triple	20	<0.01	No	None	Alive	01/2014
17	Prec B	141	78	Y	01/2011	4.0F	NH t(9;12)	Dex	HD	n/a	Single	5	<0.01	Yes	Relapse	Alive	01/2014
18	Prec B	0.8	9	N	10/2012	3.9F	NH	Dex	HD	Single	Triple	20	0.066	No	None	Alive	09/2013
19	ETP	4.5	24	N	01/2013	3.6F	NH	Pred	HD	n/a	Single	20	2.6	Yes	TRM	Deceased	11/2013

Prec B, Precursor B; Genetics-NH, not hyperdiploid karyotype; H, hyperdiploid karyotype; DT, double trisomies 4, 10; Dex, dexamethasone; Pred, prednisone; HD, high dose; CR, complete remission/alive at time of last follow up; Escal, escalating; DI, delayed intensification; D29 MRD, day 29 minimal residual disease in the bone marrow; HSCT, hematopoietic stem cell transplant; N/a, not applicable (regarding treatment, some patients did not receive this phase of therapy or did not receive HD MTX); ND, not done (depending on treatment era, may not have been widely available or issue with diagnostic specimen); TRM, treatment-related mortality; ETP, early precursor T ALL; WBC, white blood cell count at diagnosis [a]Event: death from any cause, progression, relapse or secondary malignancy. [b]During induction. [c]Interim maintenance methotrexate dose regimen. Cumulative doses reported only for high-dose methotrexate. [d]Triple IT: those patients that received at least some triple intrathecal chemotherapy; may have been combined with single IT. [e]CNS + based on abnormal neuro-imaging.

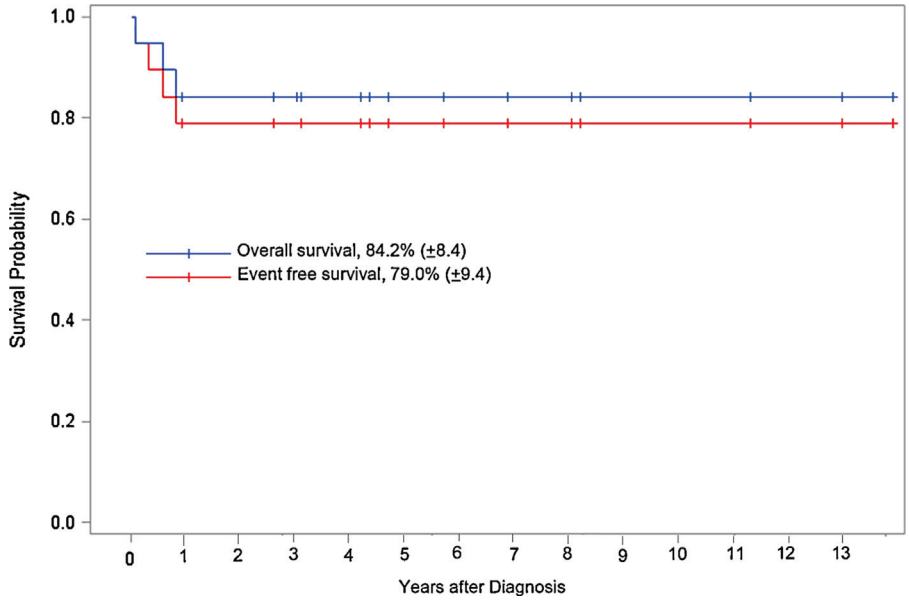

Fig. 1. Event-free and overall survival of study cohort.

CNS relapse with the omission of CRT, they had failed to maintain favorable EFS and OS, perhaps owing to inadequate systemic therapy.[12,13] More recently, the St. Jude total therapy XIV and XV trials have been able to maintain both favorable survival rates and low cumulative risk of CNS relapse with intensification of intrathecal and systemic chemotherapy alone.[8,14] However, in the Total XV trial, when compared to the overall cohort, patients with overt CNS leukemia had a significantly lower EFS (43.2 vs. 85.6% 5-year EFS) and experienced a substantial number of adverse events with an inferior OS (71.1 vs. 93.5%).[8]

A variety of approaches have been utilized for the intensification of CNS-directed chemotherapy in pediatric patients with ALL including triple intrathecal chemotherapy, high-dose methotrexate, intensified asparaginase, and dexamethasone.[8,15–17] In our group of patients, at least one of these strategies was used in the majority of patients in the context of systemic chemotherapy based on COG protocols. The type of intensification was based on treating physician preference. Intensification of systemic and intrathecal therapy did not appear to be associated with an unfavorable outcome in those patients who did not proceed to transplant. TRM was mainly associated with HSCT. There was one death among the 17 patients who did not proceed to HSCT in first remission. This patient was suspected to have an undiagnosed chromosome fragility disorder, and died as a complication of chemotherapy-induced bone marrow failure soon after induction. The cumulative risk of CNS relapse in our patient cohort was 5.2%. Only one patient developed a very early isolated CNS relapse, diagnosed on day 1 of interim maintenance, prior to the time point when CRT is usually

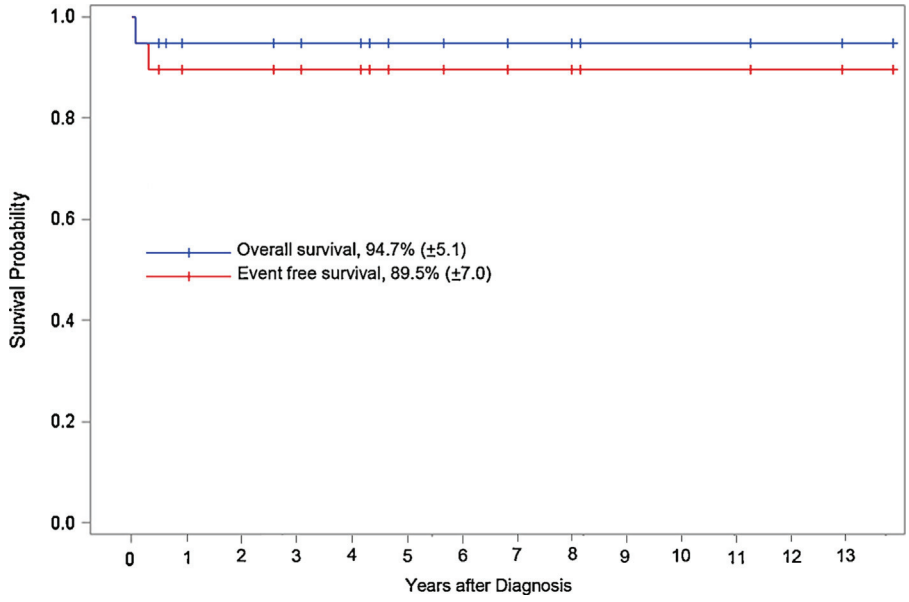

Fig. 2. Event-free and overall survival of study cohort, censored at the time of transplant.

administered. The majority of events in our cohort were related to treatment-related mortality after intensification of treatment secondary not to CNS positivity but other high risk characteristics (Philadelphia chromosome or ETP phenotype).

Our study has several limitations including its retrospective nature, small sample size, and heterogeneity of intensification strategies. Children with T-ALL were also under-represented and hence limits are ability to extrapolate our data to this population. Also, several patients lacked MRD data. Nonetheless, our results suggest that omission of CRT from the treatment of young children with CNS leukemia, at least those with B-ALL, when treated with augmented BFM protocols and intensified CNS-directed chemotherapy, does not result in increased CNS relapse rate and decreased survival. These findings may be of use when counseling the caregivers of young children with CNS leukemia about the benefits and risks of CRT. We suggest confirmation of our findings by prospective multi-center clinical trials, which should also assess the late neurocognitive deficits that are associated with intensified systemic and intrathecal chemotherapy and potentially explore whether CRT can be safely omitted in children >5 years of age with CNS-3 disease.

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