

## Scientific Article

# Optimizing Management of the Central Nervous System in Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Stem Cell Transplantation



Pranalee Patel, BS,<sup>a</sup> Mairead Dillon, BS,<sup>b</sup> Donna Niedzwiecki, PhD,<sup>b</sup> Mitchell E. Horwitz, MD,<sup>c</sup> and Chris R. Kelsey, MD<sup>a,\*</sup>

<sup>a</sup>Departments of Radiation Oncology, Duke University Medical Center, Durham, North Carolina; <sup>b</sup>Biostatistics and Bioinformatics, Duke University Medical Center, Durham, North Carolina; and <sup>c</sup>Medicine, Division of Hematologic Malignancies and Cellular Therapy, Duke University Medical Center, Durham, North Carolina

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## Abstract

**Purpose:** To evaluate clinical outcomes and patterns of failure, specifically in regards to the central nervous system (CNS), in patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic hematopoietic stem cell transplantation (HSCT) using total body irradiation (TBI)-based conditioning regimens.

**Methods and Materials:** All adult patients (aged  $\geq 18$  years) with ALL undergoing allogeneic HSCT using TBI-based conditioning regimens treated from 1995 to 2020 at Duke University Medical Center were evaluated. Various patient, disease, and treatment-related factors were collected, including CNS prophylaxis and treatment interventions. Clinical outcomes, including freedom from CNS relapse, were calculated using the Kaplan-Meier method for patients with and without CNS disease at presentation.

**Results:** One hundred and fifteen patients with ALL were included the analysis (myeloablative, 110; nonmyeloablative, 5). Of the 110 patients undergoing a myeloablative regimen, most ( $n = 100$ ) did not have CNS disease before transplant. For this subgroup, peritransplant intrathecal chemotherapy was administered in 76% (median of 4 cycles) and 10 received a radiation boost to the CNS (cranial irradiation, 5; craniospinal, 5). Only 4 failed in the CNS after transplant, none of whom received a CNS boost, with freedom from CNS relapse at 5 years of 95% (95% confidence interval (CI), 84-98%). Freedom from CNS relapse was not improved with a radiation therapy boost to the CNS (100% vs 94%,  $P = .59$ ). Overall survival, leukemia-free survival, and nonrelapse mortality at 5 years were 50%, 42%, and 36%, respectively. Among the 10 patients with CNS disease before transplant, 10 of 10 received intrathecal chemotherapy and 7 received a radiation boost to the CNS (cranial irradiation, 1; craniospinal, 6) and none subsequently failed in the CNS. A nonmyeloablative HSCT was pursued for 5 patients because of advanced age or comorbidities. None of these patients had prior CNS disease or received a CNS or testicular boost, and none failed in the CNS after transplant.

**Conclusions:** A CNS boost may not be necessary in patients with high-risk ALL without CNS disease undergoing a myeloablative HSCT using a TBI-based regimen. Favorable outcomes were observed with a low-dose craniospinal boost in patients with CNS disease.

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Research data are stored in an institutional repository and will be shared upon reasonable request to the corresponding author.

\*Corresponding author: Chris R. Kelsey, MD; E-mail: [Christopher.kelsey@duke.edu](mailto:Christopher.kelsey@duke.edu)

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## Introduction

The central nervous system (CNS) is an important sanctuary site for acute lymphoblastic leukemia (ALL) and is involved at diagnosis in 5% to 7% of patients.<sup>1,2</sup> Further, approximately 30% to 50% of adults will experience CNS failure after achieving a marrow remission without appropriate prophylaxis.<sup>3,4</sup> Because of these observations, effective CNS treatment and prophylaxis is an integral component of adult ALL treatment regimens. Numerous approaches have developed over time to address CNS disease including high-dose systemic chemotherapy, intrathecal (IT) chemotherapy, and various radiation therapy (RT) interventions including cranial (CrI) and craniospinal irradiation (CSI).<sup>5</sup> While systemic and IT therapies are routinely implemented in modern treatment programs, there remains some uncertainty about how RT should be incorporated, particularly in patients with known CNS involvement at diagnosis.<sup>6</sup>

Patients with high-risk ALL, including those with CNS involvement, often undergo hematopoietic stem cell transplantation (HSCT). Total body irradiation (TBI) is routinely used as part of the conditioning regimen, in part because of its ability to treat sanctuary sites that might harbor occult disease including the CNS and testes.<sup>7-9</sup> Many patients will also undergo an additional RT boost to the CNS or testicles before or during TBI. However, there remains some uncertainty whether additional RT to the CNS axis is beneficial in patients without known CNS involvement, and there is wide practice variation regarding RT recommendations in patients with known CNS disease, including field size (CrI vs CSI) and dose.<sup>10-12</sup>

As patients undergoing HSCT are typically young, optimization of treatment regimens is crucial to both provide durable disease control and reduce the risk of long-term toxicity. As RT utilization in ALL varies significantly, we reviewed our institutional experience managing patients with ALL, with and without CNS involvement, who underwent HSCT using TBI-based conditioning regimens. At our institution we have generally used lower doses than have been used historically, providing a unique opportunity to explore this issue further.

## Methods and Materials

After receiving approval from our institutional review board, all adult patients ( $\geq 18$  years) with ALL undergoing allogeneic HSCT using a TBI-based conditioning regimen between January 1, 1995 and December 31, 2020 were evaluated. Patients undergoing both ablative and nonmyeloablative regimens were included. Various patient and treatment-related factors were collected including demographics, disease phenotype (cytogenetics, white blood count [WBC] at diagnosis, cell of origin), CNS

involvement at diagnosis, receipt of peritransplant IT chemotherapy (pre- and posttransplant), prior CNS radiation, remission status before transplant, TBI regimen and boost information, and donor source.

TBI was delivered using a uniform technique throughout the study period using opposed lateral fields with the patient in a recumbent position, arms at sides. Custom brass compensators for the head, neck, and legs were used to provide uniform dose homogeneity ( $\pm 5\%$ ). All patients undergoing ablative TBI had the lung dose attenuated using the arms with additional brass compensators as required. The degree of lung attenuation (typically 7-10 Gy) was determined individually by the treating physician based on pulmonary function tests and other clinical factors. An acrylic spoiler was placed between the beam and the patient to increase skin dose. Photon energies of 4 MV or 6 MV were employed using a dose rate of 15 to 20 cGy per minute. Patients undergoing myeloablative TBI received 12 to 13.5 Gy in 1.5 Gy bid fractions. Those undergoing nonmyeloablative HSCT received 2 Gy in a single fraction.

CNS boosts, using either CrI or CSI, were delivered immediately before initiating TBI. CrI was given using opposed lateral fields. The spine was treated using 2 matched posterior-anterior fields. Males undergoing a testicular boost (2 Gy  $\times$  2) were treated while receiving TBI using a single anterior oblique 6X photon beam using 1.5 cm of bolus with the dose prescribed to Dmax, either on consecutive days, or more recently, on divided days. Whether a patient received a CNS boost or not, as well as the technique and dose used, were at the discretion of the treating physicians and not standardized over the period.

For patients undergoing ablative HSCT, high-dose chemotherapy was given after TBI and consisted of various regimens, most commonly cyclophosphamide ( $n = 30$ , 30%) or etoposide ( $n = 22$ , 22%). For patients undergoing nonmyeloablative regimens, chemotherapy preceded TBI and most commonly consisted of cyclophosphamide and fludarabine with either antithymocyte globulin or alemtuzumab.

## Statistical analyses

Patients were divided into 3 categories based on their disease status and treatment strategy. Cohort 1 included patients with ALL undergoing myeloablative transplant without CNS disease at diagnosis ( $n = 100$ ); cohort 2 were those undergoing myeloablative transplant with CNS disease at diagnosis ( $n = 10$ ); and cohort 3 included those undergoing a nonmyeloablative transplant ( $n = 5$ ). Descriptive statistics were computed for baseline patient, disease, and treatment characteristics. For each cohort, overall survival (OS) was measured from transplant date to date of death or date of last follow-up with death as an event. Leukemia-free survival (LFS) was measured as date

of transplant to date of relapse or death with dates of relapse and death as the events and patients who did not relapse or die censored at last follow-up. Nonrelapse mortality (NRM) was calculated as date of transplant to date of death with death as the event. Patients who relapsed were censored at time of relapse while patients who did not relapse or die were censored at last follow-up. Kaplan-Meier estimates (KM) were obtained for OS and LFS. NRM was estimated as cumulative incidence.

For each cohort, 5-year KM survival estimates for OS, LFS, and the cumulative incidence of NRM were calculated with 95% CIs. For cohort 1, freedom from CNS relapse was calculated from time of transplant to date of CNS relapse. Patients without CNS relapse were censored at date of death, last follow-up, or date of relapse in the absence of CNS failure. CNS relapse was defined as any of the following: clinical symptoms of CNS relapse, leukemic blasts in the cerebrospinal fluid, or contrast-enhancing brain or spinal lesion(s) consistent with leukemic involvement. The 5-year survival estimates for freedom from CNS relapse were calculated by KM, overall and by whether or not the patient had a CNS boost. The median follow-up time and range were calculated for each cohort among surviving patients. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

## Results

Between 1995 to 2020, 115 patients with ALL underwent allogeneic HSCT using a TBI-based conditioning regimen and were included in the analysis. A myeloablative conditioning regimen was used in 110. Among these, 100 did not have evidence of CNS involvement at diagnosis and 10 had documented CNS disease. These 2 groups were analyzed separately. The remaining 5 patients underwent a nonmyeloablative regimen. Patient characteristics can be found in [Table 1](#).

### Myeloablative: CNS negative (n = 100)

Peritransplant IT chemotherapy was administered to 75 patients (75%) with a median number of 4 administrations (range, 1-18). A radiation boost to the CNS was given immediately before TBI to 10 patients (10%). Radiation consisted CrI in 5 patients (5%) and CSI in 5 (5%) patients. The median dose to the brain was 5.4 Gy (range, 4.5-24) and the median dose to the spine was 4.5 Gy (range, 4.5-10.8). All 10 patients who received CrI or CSI also received IT chemotherapy. A testicular boost was used in 97% of male patients. This cohort included 2 patients who received prophylactic cranial irradiation as part of their initial course of therapy and then underwent HSCT at the time of relapse (1 and 11 years later). These courses of RT were not considered part of their HSCT

regimen, and neither of these patients received a CNS boost with their regimen.

Median follow-up of living patients in this cohort was 6 years (range, 0.3-24). A CNS relapse developed in 4 of 100 (4%) patients during the follow-up period ([Table 2](#)). Three relapses were isolated to the CNS. Freedom from CNS relapse was 95% (95% CI, 84-98%) at 5 years. Freedom from CNS relapse was not improved with an RT boost to the CNS compared with no boost (100% vs 94%,  $P = .59$ ) ([Fig. 1](#)). All 4 patients who failed in the CNS received further CNS-directed therapy but ultimately died (2 from CNS disease and 2 from complications from further therapy). No male patients failed in the testicles. OS, LFS, and NRM at 5 years was 50% (95% CI, 39-60%), 42% (95% CI, 32-52%), and 36% (95% CI, 26-47%), respectively.

### Myeloablative: CNS positive (n = 10)

CNS positive disease consisted of positive cytology only in 6 patients, positive cytology and imaging abnormalities in 2 patients, and imaging abnormalities without positive cytology in 2 patients. All 10 patients received IT chemotherapy (median administrations, 6; range, 5-12) before transplant, with 9 of 10 (90%) clearing the CNS. Two patients received additional posttransplant IT chemotherapy. An RT boost was used in 7 patients (70%). Radiation consisted CrI in 1 patient and CSI in 6 patients. The median dose to the brain was 5.4 Gy (range, 3-19.5) and the median dose to the spine was 6 Gy (range, 1.3-19.5). A testicular boost was used in 80% of male patients. This cohort included 2 patients who received cranial irradiation as part of their initial course of therapy and then underwent HSCT at the time of relapse (1 and 2 years later). Both of these patients received an additional CNS boost at the time of relapse.

Median follow-up of living patients in this cohort was 2 years (range, 1-10). There were no CNS relapses during the follow-up period. There were no testicular failures in male patients. OS, LFS, and NRM at both 2 and 5 years were 45% (95% CI, 13-73%), 45% (95% CI, 13-73%), and 55% (95% CI, 26-83%).

When comparing patients with (n = 10) and without (n = 100) CNS involvement, there were no differences in OS (45% vs 50%,  $P = .77$ ) ([Fig. 2](#)) or LFS (45% vs 42%,  $P = .78$ ).

### Nonmyeloablative: All patients (n = 5)

No patients undergoing a nonmyeloablative HSCT had CNS disease before transplant ([Table 3](#)). Peritransplant IT chemotherapy was administered to 4 of 5 patients (80%) with a median number of 4 administrations (range, 1-4). No patients received an RT boost to either the CNS or

**Table 1 Patient characteristics**

Characteristic	Myeloablative (n = 110)		Nonmyeloablative (n = 5)
	CNS – (n = 100)	CNS + (n = 10)	
Median age* (range)	41 (19-65)	38 (25-45)	58 (44-62)
Sex			
Male	62 (62%)	5 (50%)	0 (0%)
Female	38 (38%)	5 (50%)	5 (100%)
Phenotype			
B-cell	79 (79%)	6 (60%)	3 (60%)
T-cell	17 (17%)	4 (40%)	2 (40%)
Mixed	4 (4%)	0 (0%)	0 (0%)
t(9;22) (Philadelphia chromosome)	39 (39%)	3 (30%)	1 (20%)
Elevated WBC count at diagnosis <sup>†</sup>			
Yes	34 (34%)	1 (10%)	0 (0%)
No	53 (53%)	6 (60%)	N/A
Unknown	13 (13%)	3 (30%)	N/A
Disease status at transplant			
CR1	64 (64%)	3 (30%)	1 (20%)
CR2	32 (32%)	6 (60%)	2 (40%)
Other	4 (4%)	1 (10%)	2 (40%)
Testicular involvement at diagnosis (males only)	0/62 (0%)	0/5 (0%)	N/A
Type of transplant			
Sibling	34 (34%)	5 (50%)	3 (60%)
Matched unrelated donor	34 (34%)	3 (30%)	0 (0%)
Umbilical cord blood	30 (30%)	2 (20%)	2 (40%)
Haploidentical/Other	2 (2%)	0 (0%)	0 (0%)
IT chemotherapy			
No	25 (25%)	0 (0%)	1/5 (20%)
Yes	75 (75%)	10/10 (100%)	4/5 (80%)
Pretransplant doses, median (range)	3 (1-9)	6 (5-12)	2 (1-3)
Posttransplant doses, median (range)	4 (2-9)	2.5 (1-4)	1.5 (1-2)
Testicular boost (4 Gy) (males only)	60/62 (97%)	4/5 (80%)	N/A
CNS boost	10 (10%)	7 (70%)	0 (0%)
Cranial boost	5 (5%)	1 (10%)	N/A
Craniospinal boost	5 (5%)	6 (60%)	N/A
Cranial dose, median (range)	5.4 (4.5-24)	5.4 (3-19.5)	N/A
Spinal dose, median, (range)	4.5 (4.5-10.8)	6 (1.3-19.5)	N/A

*Abbreviations:* ALL = acute lymphoblastic leukemia; CNS = central nervous system; CR = complete remission; IT = intrathecal; N/A = not applicable; t = translocation; WBC = white blood count.

\*at transplant

<sup>†</sup>>100k for T-cell, >30k for B-cell ALL.

testicles. Median follow-up among living patients was 9.7 years (range, 4-16). There were no CNS or testicular relapses during the follow-up period in this cohort. OS and LFS at 2 and 5 years were both 40% (95% CI, 5-75%).

## Discussion

In our experience, patients with high-risk ALL without CNS disease undergoing a TBI-based conditioning

regimen before transplant are at low risk of failing in the CNS. Further, an RT boost to the brain or spine in this cohort did not improve outcomes. A large proportion of the CNS negative patients received IT chemotherapy in addition to approximately 13.5 Gy TBI. This seems to be adequate to control potential occult disease. The much smaller cohort of patients with CNS positive disease were treated with a variety of CNS-directed therapies, but almost all patients received both IT chemotherapy and an RT boost to the CNS. In this group, there were no CNS

**Table 2** Characteristics of patients with CNS relapse after transplantation

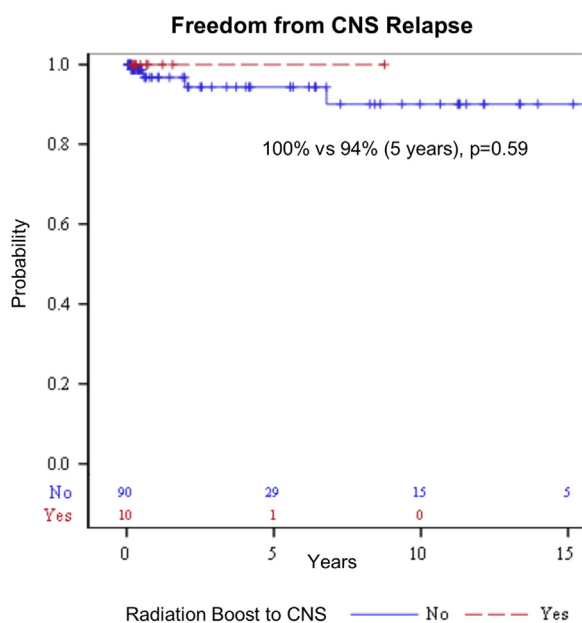
Patient	Age	CNS risk factors	IT chemotherapy administrations			Days from HSCT to CNS relapse	Additional relapse site
			Pretransplant	Post-transplant	Transplant specifics		
1	30	None	3	0	CR1; myeloablative; matched sibling; no CNS boost	2480	None
2	44	Elevated WBC t(9;22) (Philadelphia chromosome)	5	3	CR1; myeloablative; matched sibling; no CNS boost	209	None
3	26	None	6	6	R/R; myeloablative; matched sibling; no CNS boost	724	None
4	25	None	0	0	CR2; myeloablative; matched unrelated donor; no CNS boost	54	Hematologic

*Abbreviations:* CNS = central nervous system; CR = complete remission; HSCT = hematopoietic stem cell transplant; IT = intrathecal; R/R = relapsed/refractory; t = translocation; WBC = white blood count.

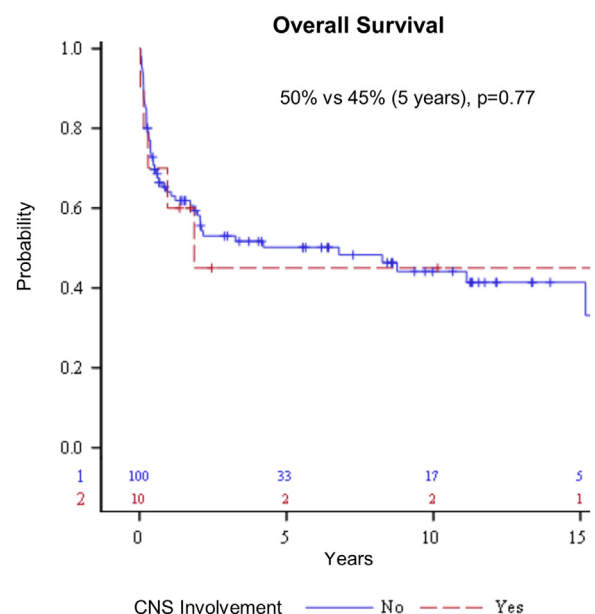
failures and outcomes mirrored the CNS negative cohort. The vast majority of patients undergoing HSCT at our institution received a myeloablative conditioning regimen (96%). A select number of patients underwent a nonmyeloablative conditioning regimen (none of whom had CNS disease at diagnosis nor received a CNS boost) without any CNS recurrences.

The CNS requires special consideration in ALL. Disease is present in the cerebrospinal fluid or brain

parenchyma at diagnosis in 5% to 7% of patients<sup>1,2</sup> and approximately 30% to 50% of adults will relapse in the CNS after achieving a marrow remission without appropriate prophylaxis.<sup>3,4</sup> Even with prophylaxis, 10% to 12% of patients will fail in the CNS, half of which are isolated recurrences.<sup>1</sup> Multiple studies have identified independent high-risk features for the development of CNS disease including younger age, hyperleukocytosis, high-risk cytogenetics, and cellular phenotype.<sup>13</sup> CNS-directed



**Figure 1** Freedom from central nervous system (CNS) relapse in patients with acute lymphoblastic leukemia without CNS involvement at diagnosis who received, or did not receive, a radiation boost to the CNS.



**Figure 2** Overall survival in patients with acute lymphoblastic leukemia with and without central nervous system involvement at diagnosis.



**Table 3** Patients undergoing nonmyeloablative transplant

Patient	Age/ Sex	CNS risk factors	IT chemotherapy administrations		Transplant specifics	Reason for nonmyeloablative HSCT	Disease outcomes
			Pre-HSCT	Post- HSCT			
1	64	t(9;22) (Philadelphia chromosome)	1	0	CR1; matched sibling; Flu/Cy/MoAb CD52; no CNS boost	Age	No CNS relapse; nonrelapse mortality at 6 mo
2	44	None	2	2	CR2; UCB; Flu/Cy/ATG; no CNS boost	Prior myeloablative TBI	No CNS relapse; hematologic remission at 15 y
3	62	None	3	1	CR2; matched sibling; Flu/Cy/MoAb CD52; no CNS boost	Patient preference	No CNS relapse; hematologic relapse at 2 mo
4	58	None	0	0	R/R; matched sibling; Flu/Cy; no CNS boost	Impaired pulmonary function	No CNS relapse; hematologic remission at 4 y
5	42	None	NS	NS	R/R; UCB; Flu/Cy/ATG; no CNS boost	Impaired pulmonary function	No CNS relapse; hematologic relapse at 1 mo

*Abbreviations:* ATG = antithymocyte globulin; CNS = central nervous system; CR = complete remission; Cy = cyclophosphamide; Flu = fludarabine; HSCT = hematopoietic stem cell transplant; IT = intrathecal; MoAb CD52 = alemtuzumab; NS = not stated; R/R = relapsed/refractory; t = translocation; TBI = total body irradiation.

therapies, such as IT chemotherapy, high-dose systemic therapy, and RT, play a key role in both the prevention and treatment of CNS disease. While IT and high-dose systemic chemotherapy have largely replaced RT in the prophylactic setting, RT continues to play an important role in CNS positive disease, particularly in adults.

Adults with high-risk ALL often undergo HSCT. TBI has been shown to be an important component of the conditioning regimen and provides a dose of 12 to 14 Gy to the craniospinal axis.<sup>7,14</sup> While some studies suggest that CNS irradiation can be replaced with high-dose systemic or IT chemotherapy in certain risk groups,<sup>15</sup> it is not well understood which patients might benefit from additional RT to the CNS, whether that should be administered to the brain only or to the entire craniospinal axis, what total dose is optimal,<sup>16</sup> and how IT and high-dose chemotherapy regimens may influence these questions.<sup>17</sup>

Studies have not always provided concordant conclusions on many of these issues, including the role of a CNS boost in patients without CNS disease at diagnosis. A retrospective study from the University of Arizona evaluated 58 patients with high-risk ALL, none of whom had CNS disease at diagnosis, who underwent an allogeneic HSCT using a uniform myeloablative TBI-based conditioning regimen (12 Gy/6 fractions).<sup>11</sup> All patients received prophylactic IT chemotherapy in addition to systemic therapy. A low-dose (6 Gy) cranial boost was associated with improved CNS-relapse free survival at 7 years (100% vs 76%,  $P = .04$ ), but this did not translate to improved PFS

or OS, likely because most patients (4/6) who relapsed in the CNS had a simultaneous marrow failure.

Another study from the Icahn School of Medicine at Mount Sinai evaluated 43 adult (>15 years) patients with high-risk ALL without CNS involvement undergoing HSCT.<sup>12</sup> CNS failure occurred in 0 of 27 (0%) patients who received a 6 Gy cranial boost and 2 of 16 (12.5%) who did not. IT chemotherapy was given to 63% and 69% of each cohort, respectively. However, the TBI dose varied between the 2 groups. All patients who received a cranial boost also received myeloablative TBI (12–15 Gy), while many of the patients who did not receive a cranial boost underwent a nonmyeloablative HSCT with low-dose TBI, suggesting that the beneficial effect of a cranial boost might have resulted from lower doses of TBI.

In contrast, a large retrospective study from the University of Minnesota evaluated 160 patients with ALL without CNS involvement, all of whom underwent myeloablative TBI (13.2 Gy).<sup>10</sup> Pretransplant IT chemotherapy utilization was not described. Among 160 patients without CNS involvement, none of whom received a cranial boost, only 4 (2.5%) failed in the CNS. Our study showed similar findings with 4 of 90 (4%) patients failing in the CNS without a cranial boost. Similar to the University of Minnesota study, all patients at our institution received a myeloablative dose of TBI and most (76%) received pretransplant IT chemotherapy.

Patients with a history of CNS involvement may require additional treatment to clear this compartment

of residual disease. Indeed, several studies, including our own, have shown that a cranial or CSI boost is used more frequently in this cohort compared with patients without CNS involvement.<sup>10,12</sup> In the study from the University of Minnesota, among 41 patients with documented CNS involvement who were eligible for a CNS boost, the 2-year risk of CNS failure was 0% with a cranial boost versus 21% without ( $P = .03$ ). The cranial boost dose ranged from 9 to 10 Gy, given in addition to 13.2 Gy TBI. This is consistent with our findings in which no patients with prior CNS involvement failed in the CNS with 100% of patients receiving peritransplant IT chemotherapy and 70% of patients receiving a boost consisting of CrI or CSI. In the study from Icahn School of Medicine, of 12 patients with prior CNS disease, only 1 relapsed within the CNS after receiving a cranial boost. While the optimal dose and field remain uncertain in this setting, it seems appropriate to pursue an RT boost to the CNS in such patients.

As with all retrospective studies addressing relatively rare diseases, especially when exploring nuances of treatment, there are limitations that must be considered. While the number of patients in our study without CNS involvement was quite robust, we only had 10 patients with known CNS disease, which limits definitive conclusions for this subgroup. Further, with only 4 relapses in the CNS, it was challenging to formally evaluate potential prognostic variables such as cell of origin, age, et cetera. We were also unable to optimally evaluate the risks of additional RT in these patients given the retrospective nature of the analysis. Strengths of our study include a homogeneous TBI-based transplant regimen using a consistent dose, a large number of CNS negative patients, and thorough reporting of other variables including IT chemotherapy administration.

## Conclusions

Taken together, we would conclude that for adult patients with high-risk ALL undergoing an allogeneic HSCT using a myeloablative TBI-based conditioning regimen, utilization of a CNS boost is most beneficial in patients with prior CNS involvement. In patients without prior CNS disease who receive peritransplant IT chemotherapy, with a TBI dose of 12 to 14 Gy, additional RT to the brain or spine seems unnecessary. Our results support current guidelines provided by the International Lymphoma Radiation Oncology Group that recommend an RT boost only in CNS + patients.<sup>6</sup> In patients with known CNS involvement, a total dose of approximately 18 Gy to the CNS (TBI and RT boost) seems sufficient to provide excellent outcomes. Whether a boost to just the brain or the entire craniospinal axis is optimal remains unclear. Most patients (6/7) in our study receiving a CNS boost received CSI.

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