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

Pranalee Patel B.S. , Mairead Dillon B.S. , Donna Niedzwiecki Ph.D. , Mitchell E. Horwitz M.D. , Chris R. Kelsey M.D.

PII: S2452-1094(22)00188-9
DOI: https://doi.org/10.1016/j.adro.2022.101082
Reference: ADRO 101082

To appear in: Advances in Radiation Oncology

Received date: 7 September 2022
Accepted date: 15 September 2022

Please cite this article as: Pranalee Patel B.S. , Mairead Dillon B.S. , Donna Niedzwiecki Ph.D. , Mitchell E. Horwitz M.D. , Chris R. Kelsey M.D. , Optimizing Management of the Central Nervous System in Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Stem Cell Transplantation, Advances in Radiation Oncology (2022), doi: https://doi.org/10.1016/j.adro.2022.101082
Optimizing Management of the Central Nervous System in Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Stem Cell Transplantation

Pranalee Patel, B.S.¹, Mairead Dillon, B.S.², Donna Niedzwiecki, Ph.D.², Mitchell E. Horwitz, M.D.³, Chris R. Kelsey, M.D.¹

Departments of Radiation Oncology¹, Biostatistics and Bioinformatics², and Medicine, Division of Hematologic Malignancies and Cellular Therapy³, Duke University Medical Center, Durham, NC 27710

Short Running Title: Managing the CNS in ALL

Keywords: acute lymphoblastic leukemia, central nervous system, cranial boost, craniospinal irradiation, allogeneic stem cell transplantation

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

Corresponding Author:
Chris R. Kelsey, M.D.
Duke University Medical Center
DUMC Box 3085
Durham, NC 27710 USA
919-668-5214 (phone)
919-668-7345 (fax)
Christopher.kelsey@duke.edu

Statistical Author:
Donna Niedzwiecki, Ph.D.
Duke University Medical Center
919-681-5030 (phone)
Donna.niedzwiecki@duke.edu

Conflicts of Interest Notification- None of the authors of this publication have a financial interest in the content of this manuscript

Source of Financial Support- Radiation Oncology Department, Duke University

Short running title- Managing the CNS in ALL

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) utilizing total body irradiation (TBI)-
based conditioning regimens.

Materials/Methods: All adult (≥ 18 y/o) patients with ALL undergoing allogeneic HSCT utilizing
TBI-based conditioning regimens treated from 1995-2020 at XXX 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: 115 ALL patients were included the analysis (myeloablative- 110; non-myeloablative-
5). Of the 110 patients undergoing a myeloablative regimen, most (n=100) did not have CNS
disease prior to transplant. For this subgroup, peri-transplant intrathecal (IT) 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% CI, 84-98%). Freedom
from CNS relapse was not improved with an RT boost to the CNS (100% vs. 94%, p=0.59).
Overall survival, leukemia-free survival, and non-relapse mortality at 5 years were 50%, 42%,
and 36%, respectively. Among the 10 patients with CNS disease prior to transplant, 10/10
received IT chemotherapy and 7 received a radiation boost to the CNS (cranial irradiation- 1;
craniospinal- 6) and none subsequently failed in the CNS. A non-myeloablative HSCT was
pursued for 5 patients due to 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 utilizing a TBI-based regimen. Favorable outcomes were observed with a low-dose craniospinal boost in patients with CNS disease.
Introduction

The central nervous system (CNS) is an important sanctuary site for acute lymphoblastic leukemia (ALL) and is involved at diagnosis in 5-7% of patients\(^1,2\). Further, approximately 30-50% of adults will fail in the CNS after achieving a marrow remission without appropriate prophylaxis\(^3,4\). Due to 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)\(^5\). 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\(^6\).

Patients with high-risk ALL, including those with CNS involvement, often undergo hematopoietic stem cell transplantation (HSCT). Total body irradiation (TBI) is routinely utilized 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\(^7,9\). Many patients will also undergo an additional RT boost to the CNS and/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 versus CSI) and dose\(^10,12\).

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 ALL patients, with and without CNS involvement, who underwent HSCT using TBI-based
conditioning regimens. At our institution we have generally utilized lower doses than have been used historically, providing a unique opportunity to explore this issue further.

Methods & Materials

After receiving approval from our Institutional Review Board, all adult (≥18 years old) patients with ALL undergoing allogeneic HSCT utilizing a TBI-based conditioning regimen between January 1, 1995 and December 31, 2020 were evaluated. Patients undergoing both ablative and non-myeloablative 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 peri-transplant IT chemotherapy (pre- and post-transplant), 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 (+/- 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 15-20 cGy/minute. Patients undergoing myeloablative TBI received 12-13.5 Gy in 1.5 Gy bid fractions. Those undergoing non-myeloablative HSCT received 2 Gy in a single fraction.
CNS boosts, utilizing either CrI or CSI, were delivered immediately prior to initiating TBI. CrI was given using opposed lateral fields. The spine was treated using two matched PA fields. Males undergoing a testicular boost (2 Gy X 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 utilized, were at the discretion of the treating physicians and not standardized over the time 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 non-myeloablative regimens, chemotherapy preceded TBI and most commonly consisted of cyclophosphamide and fludarabine with either ATG or alemtuzumab.

Statistical Analyses

Patients were divided into three categories based on their disease status and treatment strategy. Cohort 1 included ALL patients 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 non-myeloablative 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. Non-relapse 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% confidence intervals. 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 following: clinical symptoms of CNS relapse, leukemic blasts in the CSF, and/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 NC).

Results

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

*Myeloablative- CNS negative (n=100)*
Peri-transplant 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 prior to TBI to 10 (10%) patients. Radiation consisted CrI in 5 (5%) and CSI in 5 (5%). 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 utilized 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 4/100 (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% versus 94%, p=0.59) (Figure 1). All four 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, positive cytology and imaging abnormalities in 2, and 2 patients with imaging abnormalities without positive cytology. All 10 patients received IT chemotherapy (median administrations- 6; range, 5-12) before
transplant with 9/10 (90%) clearing the CNS. Two patients received additional post-transplant IT chemotherapy. A radiotherapy boost was utilized in 7 (70%). Radiation consisted CrI in 1 and CSI in 6. 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 utilized 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=0.77) (Figure 2) or LFS (45% vs 42%, p=0.78).

Non-myeloablative All patients (n=5)

No patients undergoing a non-myeloablative HSCT had CNS disease prior to transplant (Table 3). Peri-transplant IT chemotherapy was administered to 4/5 (80%) with a median number of 4 administrations (range, 1-4). No patients received a radiotherapy boost to either the CNS or 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. Overall survival and leukemia-free survival 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 prior to transplant are at low risk of failing in the CNS. Further, an RT boost to the brain and/or spine in this cohort did not improve outcomes. A large proportion of the CNS negative patients received IT chemotherapy in addition to ~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 received both IT chemotherapy and an RT boost to the CNS. In this group, there were no CNS 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 non-myeloablative 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 (CSF) or brain parenchyma at diagnosis in 5-7% of patients\textsuperscript{1,2} and approximately 30-50% of adults will relapse in the CNS after achieving a marrow remission without appropriate prophylaxis\textsuperscript{3,4}. Even with prophylaxis, 10-12% of patients will fail in the CNS, half of which are isolated recurrences\textsuperscript{1}. Multiple studies have identified independent high-risk features for the development of CNS disease including younger age, hyperleukocytosis, high-risk cytogenetics, and cellular phenotype\textsuperscript{13}. CNS-directed therapies, such as IT chemotherapy, high-dose systemic therapy, and radiation therapy, 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 12-14 Gy to the craniospinal axis\(^7\). While some studies suggest that CNS irradiation can be replaced with high-dose systemic or IT chemotherapy in certain risk groups\(^15\), 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\(^16\), and how IT and high-dose chemotherapy regimens may influence these questions\(^17\).

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)\(^11\). 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%, \(p=0.04\)), 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 (> age 15) patients with high-risk ALL without CNS involvement undergoing HSCT\(^12\). CNS failure occurred in 0/27 (0%) patients who received a 6 Gy cranial boost and 2/16 (12.5%) who did not. IT chemotherapy was given to 63% and 69% of each cohort, respectively. However, the TBI dose varied between the two 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 non-myeloablative HSCT with low-dose TBI, suggesting that the beneficial impact 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)\textsuperscript{18}. Pre-transplant 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 4/90 (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 peri-transplant 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 utilized more frequently in this cohort compared with patients without CNS involvement\textsuperscript{10,12}. 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=0.03). The cranial boost dose ranged from 9-10 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 peri-transplant 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, etc. 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.

Taken together, we would conclude that for adult patients with high-risk ALL undergoing an allogeneic HSCT utilizing 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 peri-transplant IT chemotherapy, with a TBI dose of 12-14 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. In patients with known CNS involvement, a total dose of ~18 Gy to the CNS (TBI + 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 in our study receiving a CNS boost received CSI (6/7).

Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
References


Figure 1

Freedom from CNS Relapse

100% vs 94% (5 years), p=0.59

Radiation Boost to CNS

No

Yes

Probability

Years

0

5

10

15

0.0

0.2

0.4

0.6

0.8

1.0
### Table 1 – Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Myeloablative (n=110)</th>
<th>Non-Myeloablative (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CNS– (n=100)</td>
<td>CNS+ (n=10)</td>
</tr>
<tr>
<td>Median age* (range)</td>
<td>41 (19-65)</td>
<td>38 (25-45)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (62%)</td>
<td>5 (50%)</td>
</tr>
</tbody>
</table>

**Figure 2**

Overall Survival

50% vs 45% (5 years), p=0.77
<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>5 (50%)</th>
<th>5 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell</td>
<td>79 (79%)</td>
<td>6 (60%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>T-cell</td>
<td>17 (17%)</td>
<td>4 (40%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>4 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>9;22 translocation</strong></td>
<td>39 (39%)</td>
<td>3 (30%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td><strong>Elevated WBC count at diagnosis†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (34%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No</td>
<td>53 (53%)</td>
<td>6 (60%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (13%)</td>
<td>3 (30%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td><strong>Disease status at transplant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>64 (64%)</td>
<td>3 (30%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>CR2</td>
<td>32 (32%)</td>
<td>6 (60%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4%)</td>
<td>1 (10%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td><strong>Testicular involvement at diagnosis (males only)</strong></td>
<td>0/62 (0%)</td>
<td>0/5 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Type of transplant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>34 (34%)</td>
<td>5 (50%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td>34 (34%)</td>
<td>5 (30%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Umbilical cord blood</td>
<td>30 (30%)</td>
<td>2 (20%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Haploidentical/Other</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>IT chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25 (25%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>75 (75%)</td>
<td>10/10 (100%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>Pre-transplant doses, median (range)</td>
<td>3 (1-9)</td>
<td>6 (5-12)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Post-transplant doses, median (range)</td>
<td>4 (2-9)</td>
<td>2.5 (1-4)</td>
<td>1.5 (1-2)</td>
</tr>
<tr>
<td><strong>Testicular boost (4 Gy) (males only)</strong></td>
<td>60/62 (97%)</td>
<td>4/5 (80%)</td>
<td>N/A</td>
</tr>
<tr>
<td>CNS boost</td>
<td>10 (10%)</td>
<td>7 (70%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cranial boost</td>
<td>5 (5%)</td>
<td>1 (10%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Craniospinal boost</td>
<td>5 (5%)</td>
<td>6 (60%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Cranial dose, median (range)</td>
<td>5.4 (4.5-24)</td>
<td>5.4 (3.9-19.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Spinal dose, median (range)</td>
<td>4.5 (4.5-10.8)</td>
<td>6 (1.3-19.5)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*at transplant; †>100k for T-cell, >30k for B-cell ALL

*Abbreviations: WBC- white blood cell; CR- complete remission; CNS- central nervous system; IT- intrathecal; N/A- not applicable*
Table 2 – Characteristics of Patients with CNS Relapse after Transplantation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>CNS Risk Factors</th>
<th>IT chemotherapy administrations</th>
<th>Transplant Specifics</th>
<th>Days from HSCT to CNS Relapse</th>
<th>Additional Relapse Site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pre-transplant</td>
<td>Post-transplant</td>
<td>CR1; Myeloablative; Matched sibling; No CNS boost</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30M</td>
<td>None</td>
<td>3</td>
<td>0</td>
<td>2480</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>44M</td>
<td>Elevated WBC t(9:22)</td>
<td>5</td>
<td>3</td>
<td>209</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>26M</td>
<td>None</td>
<td>6</td>
<td>6</td>
<td>724</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>25M</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>54</td>
<td>Hematologic</td>
</tr>
</tbody>
</table>

Abbreviations: M- male; CNS- central nervous system; CR- complete remission; R/R- relapsed/refractory; HSCT- hematopoietic stem cell transplant; IT- intrathecal
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>CNS Risk Factors</th>
<th>IT chemotherapy administrations</th>
<th>Transplant Specifics</th>
<th>Reason for Non-Myeloablative HSCT</th>
<th>Disease Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64F</td>
<td>t(9;22)</td>
<td>1</td>
<td>CR1; Matched sibling; Flu/Cy/MoAb CD52; No CNS boost</td>
<td>Age</td>
<td>No CNS Relapse; Non-relapse mortality at 6 months</td>
</tr>
<tr>
<td>2</td>
<td>44F</td>
<td>None</td>
<td>2</td>
<td>CR2; UCB; Flu/Cy/ATG; No CNS boost</td>
<td>Prior myeloablative TBI</td>
<td>No CNS Relapse; Hematologic remission at 15 years</td>
</tr>
<tr>
<td>3</td>
<td>62F</td>
<td>None</td>
<td>3</td>
<td>CR2; Matched sibling; Flu/Cy/MoAb CD52; No CNS boost</td>
<td>Patient preference</td>
<td>No CNS Relapse; Hematologic relapse at 2 months</td>
</tr>
<tr>
<td>4</td>
<td>58F</td>
<td>None</td>
<td>0</td>
<td>R/R; Matched sibling; Flu/Cy; No CNS boost</td>
<td>Impaired pulmonary function</td>
<td>No CNS Relapse; Hematologic remission at 4 years</td>
</tr>
<tr>
<td>5</td>
<td>42F</td>
<td>None</td>
<td>NS</td>
<td>R/R; UCB; Flu/Cy/ATG; No CNS boost</td>
<td>Impaired pulmonary function</td>
<td>No CNS Relapse; Hematologic relapse at 1 month</td>
</tr>
</tbody>
</table>

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