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# Central Nervous System Relapse in Adults with Acute Lymphoblastic Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Central nervous system (CNS) relapse after allogeneic hematopoietic stem cell transplantation (HSCT) confers a poor prognosis in adult patients with acute lymphoblastic leukemia (ALL). Preventing CNS relapse after HSCT remains a therapeutic challenge, and criteria for post-HSCT CNS prophylaxis have not been addressed. In a 3-center retrospective analysis, we reviewed the data for 457 adult patients with ALL who received a first allogeneic HSCT in first or second complete remission (CR). All patients received CNS prophylaxis as part of their upfront therapy for ALL, but post-transplantation CNS prophylaxis practice varied by institution and was administered to 48% of the patients. Eighteen patients (4%) developed CNS relapse after HSCT (isolated CNS relapse, n = 8; combined bone marrow and CNS relapse, n = 10). Patients with a previous history of CNS involvement with leukemia had a significantly higher rate for CNS relapse ($P = .002$), and pretransplantation CNS involvement was the only risk factor for post-transplantation CNS relapse found in this study. We failed to find a significant effect of post-transplantation CNS prophylaxis to prevent relapse after transplantation. Furthermore, no benefit for post-transplantation CNS prophylaxis could be detected when a subgroup analysis of patients with ($P = .10$) and without previous CNS involvement ($P = .52$) was performed. Finally, we could not find any significant effect for intensity of the transplantation conditioning regimen on CNS relapse after HSCT. In conclusion, CNS relapse is an uncommon event after HSCT for patients with ALL in CR1 or CR2, but with higher risk among patients with CNS involvement before transplantation. Furthermore, neither the use of post-HSCT CNS prophylaxis nor the intensity of the HSCT conditioning regimen made a significant difference in the rate of post-HSCT CNS relapse.



## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective treatment for acute lymphoblastic leukemia (ALL), resulting in long-term remission [1]. Despite advances in therapy, disease progression remains the major cause of mortality after allogeneic HSCT, accounting for 20% to 50% of all deaths [2-4]. The central nervous system (CNS) is the most common extramedullary site of disease progression after transplantation in ALL [4].

Although the use of CNS prophylaxis as part of the upfront treatment for ALL has led to significant decreases in CNS relapse and improved outcomes overall [5,6], the routine use of post-HSCT prophylactic CNS therapy as a strategy to prevent CNS relapse after transplantation is still controversial. Studies that utilized post-HSCT CNS prophylaxis have reported disparate results and there is no generalized consensus regarding the role of post-transplantation CNS prophylaxis to prevent CNS relapse [7-10]. Furthermore, the increasing use of reduced-intensity transplantation conditioning therapies with possibly decreased CNS penetration makes it even more imperative that we try to understand the benefit, if any, of post-HSCT CNS prophylaxis.

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The practice of post-HSCT prophylactic CNS therapy varies from center to center. To determine the role of post-HSCT prophylactic CNS therapy in preventing CNS relapse in ALL patients, we designed a study in centers with different post-HSCT CNS therapy practice and reviewed the data of 457 patients with ALL who received first allogeneic HSCT in first or second complete remission (CR).

## PATIENTS AND METHODS

### *Population*

In this multicenter retrospective study, we studied all adult (age ≥18 years) ALL patients who underwent a first allogeneic HSCT at MD Anderson Cancer Center (MDACC), Fred Hutchinson Cancer Research Center (FHCRC), or Rabin Medical Center (RMC) in Israel between 2000 and 2011. We included all adult ALL patients who underwent transplantation in first or second CR. Before the transplantation procedure, all patients received intrathecal methotrexate (MTX), and/or cytarabine, and/or craniospinal irradiation as part of their standard induction and consolidation treatment.

### *Post-transplantation CNS Prophylaxis*

The practice of CNS disease prophylaxis varied between MDACC, FHCRC, and RMC. At MDACC, generally only patients with a previous history of CNS disease were offered post-transplantation CNS prophylaxis with intrathecal cytarabine, alternating with MTX, for 6 to 8 monthly infusions as tolerated; alternatively, they could receive craniospinal radiation therapy (dose 24 Gy in 12 daily fractions) or boost (12 Gy in 6 daily fractions) to the CNS as part of their scheduled total body irradiation (12 Gy in 4 daily fractions) at the time of transplantation conditioning. At FHCRC, all patients with and without history of CNS involvement before transplantation were routinely administered post-transplantation CNS prophylaxis, most commonly with intrathecal or intraventricular MTX for 4 to 6 doses every 2 weeks, as tolerated. Patients with CNS involvement incidentally found during the pre-transplantation evaluation that failed to clear with 1 to 2 doses of MTX received cranial-spinal irradiation immediately before or during conditioning. Similarly, at RMC, all patients, regardless of previous CNS disease, were given 4 injections of intrathecal MTX, with the first dose usually administered 1 month after transplantation. Ongoing transplantation toxicities and/or thrombocytopenia may be among the reasons for patients at FHCRC or RMC to not receive post-HSCT CNS prophylaxis.

### *Definitions*

*Relapse into the CNS* was defined as unequivocal morphologic evidence of leukemic blasts in the cerebrospinal fluid or cranial nerve palsies, or a nonhemorrhagic mass seen in cranial computed tomography or magnetic resonance imaging because of infiltration by leukemia cells. Cytogenetic abnormalities were classified based on previously published reports [11]. The intensity of the conditioning regimens were defined according to the Center for International Blood and Marrow Transplantation Research criteria [12].

### *Statistics*

We assessed the cumulative incidence of systemic and CNS relapses in a competing risks framework with a competing risk of nonrelapse death. Because data from second and subsequent relapses were not available, patients whose first relapse did not include CNS involvement were censored at the time of relapse. To analyze the association between post-HSCT CNS prophylactic therapy (which was given within the first 3 months after HSCT) and CNS relapse, we used a landmark cumulative incidence analysis, including only patients who had not relapsed or died by 3 months after HSCT; landmark analysis was not used for total relapse or survival analyses. The Fisher exact test and the Wilcoxon rank-sum test were used to compare categorical and continuous variables between patients with CNS prophylaxis and those without.

## RESULTS

### *Patient and Transplantation Characteristics*

We included 457 adult patients with ALL with a median age 38 years (range, 18 to 76 years). Characteristics of patients are presented in Table 1. Two hundred and seventy-three patients underwent transplantation in first CR and 184 in second CR. Sixty-seven patients (15%) had a history of pre-HSCT CNS involvement either at diagnosis (n = 38) or after first relapse (n = 29). The median follow-up for the 213 surviving patients was 3.0 years. Because of differing practice patterns, only 19% of patients at MDACC received post-transplantation CNS prophylaxis, in contrast to 79% of patients from FHCRC and RMC ($P < .0001$). Overall, 217 patients (47%) received post-transplantation intrathecal CNS prophylaxis with intrathecal MTX, cytarabine, or both agents for a median of 4 treatment cycles (range, 1 to 10). Two patients received prophylactic CNS radiotherapy after transplantation.

**Table 1**
Patient and Transplantation Characteristics

| Characteristic | No Post-HSCT CNS Prophylaxis (n = 238) | Received Post-HSCT CNS Prophylaxis (n = 219) | *P* Value |
|---|---|---|---|
| Center | | | < .0001 |
| MDACC | 193 | 45 | |
| FHCRC | 38 | 161 | |
| RMC | 7 | 13 | |
| Age at HSCT, median (range), yr | 38 (18-70) | 38 (19-76) | .78 |
| Sex | | | .34 |
| Female | 92 | 95 | |
| Male | 146 | 124 | |
| Lineage | | | 1.00 |
| B cell | 201 | 188 | |
| T cell | 33 | 30 | |
| Unknown | 4 | 1 | |
| Cytogenetic risk group | | | .65 |
| Good | 13 | 8 | |
| Intermediate | 86 | 87 | |
| Poor | 110 | 102 | |
| Unknown | 29 | 22 | |
| Status at HSCT | | | .002 |
| CR1 | 126 | 147 | |
| CR2 | 112 | 72 | |
| Pre-HSCT CNS disease | | | .06 |
| None | 209 | 174 | |
| At diagnosis | 15 | 23 | |
| At first relapse | 11 | 18 | |
| Missing | 3 | 4 | |
| Preparative regimen | | | .89 |
| Myeloablative | 204 | 189 | |
| Nonmyeloablative or RIC | 34 | 30 | |
| Allotype | | | .95 |
| HLA matched-related | 98 | 91 | |
| HLA matched unrelated | 86 | 80 | |
| HLA mismatched-related | 9 | 10 | |
| HLA mismatched unrelated | 45 | 38 | |
| Graft source | | | .001 |
| Bone marrow | 65 | 48 | |
| Peripheral blood | 136 | 157 | |
| Cord blood | 37 | 14 | |
| Relapse | | | .08 |
| Total | 60 | 74 | |
| CNS | 6 | 12 | |
| Graft-versus-host disease | | | |
| Acute, grades II-IV | 100 | 156 | |
| Chronic, limited, and/or extensive | 55 | 125 | |

RIC indicates reduced-intensity conditioning.

### *CNS Relapse after Transplantation*

The incidence of CNS relapse after transplantation in the entire cohort was 4%, with an incidence of 13% in patients with history of CNS involvement before transplantation. Characteristics of the 18 patients who developed CNS relapse after transplantation are described in Table 2. Among the 18 relapses, 8 were isolated CNS relapse and 10 were combined bone marrow and CNS relapse. The CNS relapses occurred at a median of 231 days (range, 38 to 1414) after HSCT. Nine of