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Perspective

ASBMT Statement on Routine Prophylaxis for Central Nervous System Recurrence of Acute Lymphoblastic Leukemia following Allogeneic Hematopoietic Cell Transplantation

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Hematologic malignancies treated with allogeneic hematopoietic cell transplantation (allo-HCT) have a variable incidence of post-transplantation central nervous system (CNS) relapse, with acute lymphoblastic leukemia (ALL) representing the most common disease histology. Although data supporting post-transplantation CNS prophylaxis for ALL in the pre-CNS penetrant systemic therapy era established this as standard practice, controversy exists regarding the role of post-transplantation CNS prophylaxis in the contemporary era. Here we review the most relevant (albeit exclusively retrospective) literature to date on the role of post-transplantation CNS prophylaxis in ALL. Given the paucity of data supporting the routine practice of post-transplantation CNS prophylaxis for ALL in the contemporary era, this position statement is anticipated to further stoke controversy and discussion within the transplantation community. Ultimately, only well-designed prospective clinical studies will elucidate the role of routine post-transplantation CNS prophylaxis.

INTRODUCTION

The genesis of central nervous system (CNS) prophylaxis of hematologic malignancies began with the early experience of combination chemotherapy when isolated CNS relapses of pediatric acute lymphoblastic leukemia (ALL) were observed in >50% of patients despite successful remission induction of systemic disease [1,2]. Depending on the presence or risk of CNS involvement at the time of diagnosis, incorporation of systemic CNS penetrant therapy, intrathecal therapy (ITT) with or without craniospinal radiotherapy (CSR) has greatly lowered the risk of isolated CNS recurrence. The risk for CNS disease and/or recurrence, along with approaches to treatment and prophylaxis at the time of diagnosis, have been described primarily for aggressive lymphoid malignancies, such as ALL, Burkitt lymphoma, lymphoblastic lymphoma, and diffuse large B-cell lymphoma (DLBCL). The role of primary or secondary prophylaxis in the setting of allogeneic hematopoietic cell transplantation (allo-HCT) for these diseases remains unclear, however. Moreover, clinical practice varies greatly among transplantation centers [3]. It should be noted that secondary prophylaxis is typically not administered following high-dose therapy and autologous transplantation for either primary or secondary central nervous system lymphoma (largely DLBCL) [4–6]. There is no literature on CNS prophylaxis following allo-HCT for hematologic malignancies outside of ALL. Therefore, we focus this brief review on the evidence to date for and against the incorporation of primary or secondary prophylaxis for ALL following allo-HCT.

CNS PENETRANT THERAPY AT THE TIME OF INDUCTION CHEMOTHERAPY

A discussion of post-transplantation CNS prophylaxis for ALL would be remiss without a brief background on and review of current CNS treatment and prevention at the time of initial diagnosis. The established practice of CNS prophylaxis for ALL has largely been modeled in the pediatric population, given

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the higher incidence of ALL in this age group compared with adults. The early experience of frequently observed isolated CNS relapses despite relatively adequate systemic control of disease eventually led to the incorporation of CSR with or without ITT, with a subsequent reduction in the incidence of CNS relapse [7]. Over time, given the high curability of this population as it relates to the ability to tolerate dose-intensive regimens relative to adults, risk-adapted models [8] for systemic therapy, ITT, and CSR have lowered the incidence of isolated CNS relapse.

In children, CSR is met with significant long-term risks related to endocrinopathies, neurocognitive defects and secondary malignancies [9]. Prospective pediatric clinical trials have demonstrated that CSR may be omitted for control of CNS relapse in ALL [10–12]. The combination of early CNS penetrant chemotherapy and i.v. methotrexate with or without high-dose cytarabine, in conjunction with intensified ITT, has resulted in a <5% incidence of isolated CNS relapse [13–15]. A notably higher (11%) incidence of isolated CNS relapse was observed in 5 consecutive Cancer and Leukemia Group B (CALGB) trials enrolling patients age 16 to 20 years [16]. Both groups incorporated radiation therapy for adolescents and young adults. In the first 4 of 5 CALGB protocols used for this comparative analysis, all patients received cranial irradiation. In Children's Cancer Group (CCG) studies if there was no CNS disease at diagnosis, 1800 cGy of cranial radiotherapy was given during the first 2 weeks of consolidation; patients with CNS disease at diagnosis received 2400 cGy to the cranium and 600 cGy to the spinal cord. The important difference in these aforementioned studies was earlier and more frequent ITT on CCG protocols, including later therapy phases, compared with the very abbreviated postinduction ITT given on CALGB protocols.

CNS PROPHYLAXIS POST-ALLO-HCT

There are no prospective, and very limited retrospective, data regarding the role of post-transplantation CNS-directed prophylactic therapy. Wide variations in clinical practice have been reported in the literature [3,17]. The Fred Hutchinson Cancer Research Center reported a retrospective analysis from 1970 to 1980 that compared 198 patients with ALL who received (n = 127) or did not receive (n = 71) CNS ITT prophylaxis in the context of total body irradiation (TBI)-based myeloablative conditioning and allogeneic bone marrow transplantation (allo-BMT) [18]. They observed a reduced incidence of CNS relapse following allo-BMT in the group that received IT methotrexate (38% versus 7%; $P < .02$). This retrospective analysis had many limitations, and it is important to note that the study was conducted in an era when induction therapy for ALL incorporating effective CNS prophylaxis had yet to be optimized, thereby resulting in greater therapeutic benefit in the use of post-allo-BMT ITT. In contrast to this initial publication, no isolated occurrences of CNS relapse were reported in a large more contemporary study from 1996 of 433 patients who received cranial irradiation before allo-BMT for ALL without post-transplantation ITT prophylaxis [19].

Two more relevant recent publications warrant closer discussion because they pertain to the modern era of intensive systemic and intrathecal therapy for ALL, as well as contemporary allo-HCT modalities that include peripheral blood stem cell grafts and varying intensities of conditioning regimens. A Japanese group reported a retrospective analysis of >1200 allogeneic transplantations performed between 1994 and 2004 for leukemia, of which 352 were for ALL [20]. They observed a relatively low incidence of CNS relapse and an isolated CNS relapse incidence of only 0.7%. Interestingly, the use of post-transplantation ITT CNS prophylaxis conferred a nonsignificant increased risk of CNS relapse for patients with ALL (6.2% for those who received ITT versus 3.7% in those who did not; $P = .17$). However, in multivariate analysis of the whole study cohort, the relative risk of experiencing CNS relapse was 2.57 (95% CI, 1.21 to 5.26; $P = .014$) in those who received ITT compared with those who did not. As the authors noted, it can be surmised that those receiving ITT prophylaxis were a more select group of patients with previous CNS ALL and thus a cohort at greater risk of post-transplantation CNS relapse. Despite this, after covariate adjustment for underlying disease, disease status at allo-HCT, and history of CNS ALL, ITT prophylaxis still adversely affected the incidence of CNS relapse. Importantly, those who received ITT had an increased incidence of leukoencephalopathy compared with those who did not (3.5% versus 0.5%; $P = .0076$).

More recently, a single-institution study from the City of Hope analyzed risk factors for post-transplantation CNS relapse among 87 children and adults with previously treated CNS involvement of ALL before transplantation [21]. In this cohort with a median age of 25.5 years, 29% of patients received pretransplantation cranial irradiation and 54% received post-transplantation ITT prophylaxis. The median number of post-transplantation ITT prophylaxis doses was 2 (range, 1 to 11). The majority of patients received TBI containing myeloablative conditioning. The use of TBI with conditioning ($P = .96$), pretransplantation cranial irradiation ($P = .91$), and post-transplantation ITT prophylaxis ($P = .33$) did not confer protection from CNS relapse post-transplantation. Finally, in the largest multicenter retrospective analysis of the role of post-transplantation ITT CNS prophylaxis, which included 452 patients age ≥18 years who underwent allo-HCT for ALL in the contemporary era (2000 to 2011) [17]. Owing to institutional practice variations, the authors were able to compare the incidence of CNS relapse in ALL as related to the inclusion or omission of post-transplantation prophylaxis. At 2 of the 3 centers involved in the study, post-transplantation CNS prophylaxis with ITT was offered to all patients, whereas in the other center, either CSR or ITT was offered only to patients with a previous history of CNS involvement in ALL. The incidence of CNS relapse was 4% in the entire cohort and 13% in those with a previous history of CNS disease, which was the sole risk factor for CNS relapse identified in the study ($P = .002$). Of the 18 patients who experienced CNS relapse, the majority (n = 10) had concurrent bone marrow relapse. There was no significant effect of post-allo-HCT ITT CNS prophylaxis in the subgroups with ($P = .10$) and without ($P = .52$) previous CNS involvement (Table 1).

ASBMT SURVEY ON CNS PROPHYLAXIS PRACTICES

We sent a brief, 2-question survey to 410 international transplantation centers, 72 of which responded (17.6%). The results of the survey are shown in Table 2. The centers were asked the following : (1) do you have standard institutional CNS prophylaxis guidelines for ALL patients following allo-HCT? and (2) would you be interested in a societal (ASBMT) guideline regarding CNS prophylaxis? To the former question, 43 of 72 (59.7%) centers stated that they had guidelines in place. To the latter question, all but 3 of the 72 centers (95.8%) centers that responded to the e-mail survey expressed interest in an ASBMT guideline.

CONCLUSION AND ASBMT PRACTICE GUIDELINE COMMITTEE POSITION STATEMENT

In conclusion, high-quality prospective data are lacking to guide the use (or nonuse) of CNS ITT prophylaxis in patients

Table 1
Summary of Key Retrospective Studies Investigating CNS Prophylaxis after Allo-HCT

Reference	Supports Post-Allo-HCT CNS Prophylaxis	Number of Patients	Comments
Thompson et al, 1986 [18]	Yes	415; 198 with ALL	Precontemporary, CNS-penetrant ALL induction therapy
Singhal et al, 1996 [19]	No	433; 116 with ALL	In all 116 patients with ALL without post-allo-BMT ITT prophylaxis; no isolated CNS relapses
Oshima et al, 2008 [20]	No	1226; 352 with ALL	Increased incidence of leukoencephalopathy in patients receiving ITT prophylaxis post-allo-HCT
Hamdi et al, 2014 [17]	No	457 with ALL	Largest multicenter study; only 8 patients experienced isolated CNS relapse, most frequently in patients with previous CNS involvement
Aldoss et al, 2016 [21]	No	87 with ALL	Most contemporary single-center experience exclusively addressing secondary CNS prophylaxis

Table 2
Survey Results

Variable	% Yes (n/N)
Survey response rate	17.6 (72/410)
Survey questions	
1) Do you have standard institutional CNS prophylaxis guidelines for ALL patients following allo-HCT?	59.7 (43/72)
2) Would you be interested in a societal (ASBMT) guideline regarding CNS prophylaxis?	95.8 (69/72)

with ALL undergoing allo-HCT in complete remission. Furthermore, the role of CNS prophylaxis in the era of effective and novel therapies in patients with relapsed/refractory disease before allo-HCT (eg, CAR T cells, inotuzumab for B cell ALL) is an unanswered question. The current evidence for the contemporary treatment era reported in the literature does not support routine post-transplantation CNS prophylaxis for ALL. The ASBMT encourages well-designed and appropriately powered studies to address this important clinical question.

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