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Timing and Utility of Relapse Surveillance after Allogeneic Hematopoietic Cell Transplantation in Children with Leukemia

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The utility and optimal timing of routine bone marrow (BM) and cerebrospinal fluid (CSF) surveillance after allogeneic hematopoietic cell transplantation (alloHCT) in children with leukemia have not been previously studied. To examine the current practice concerning relapse surveillance in this population, we conducted a national survey of pediatric bone marrow transplant physicians. Sixty-two of 152 potential participants (41%) completed the survey. For acute lymphoblastic leukemia (ALL) patients, 41 physicians (66%) reported performing routine BM analysis in all such patients, 15 (24%) in some patients and 6 (10%) in no patients. Data were similar for acute myeloid leukemia (AML). Among those who do such screening in the ALL population, 11 physicians (24%) reported performing 1 BM analysis in the first year, 11 (24%) performed 2, 6 (13%) performed 3, 12 (27%) performed 4, and 5 (12%) performed 5 to 10. Data were similar for AML. The most common time point for screening in both diseases was day 100, followed closely by day 365. With respect to central nervous system (CNS) screening in ALL, 11 physicians (18%) screened all patients, 28 (45%) screened no patients, and 23 (37%) screened only patients with prior CNS disease. Use of intrathecal chemotherapy in these patients also varied, with 7 (12%) doing so in all patients, 17 (29%) only in previously CNS-positive patients, and 35 (59%) in no patients. To assess the utility of surveillance procedures, we performed a retrospective review of 108 childhood leukemia patients after alloHCT at our center. Forty-one relapses (38%) occurred with a median time to relapse of 171 days. Five (12%) occurred after day 365. Of the 36 relapses within the first year, 20 (56%) were identified by clinical suspicion, whereas 16 (44%) were identified by routine screening procedures. The percentages of patients in whom routine screening detected relapse at days 100, 180, 270, and 365, respectively, was 6.7%, 11.1%, 11.9%, and 0%. That is, by day 365, no patient (of 38) who had routine BM surveillance had evidence of relapse on analysis of the BM. Our survey confirms a lack of standardization regarding routine BM and CSF relapse surveillance after alloHCT in children with leukemia. We have demonstrated that while day 365 post-alloHCT is a very commonly utilized time point for routine screening, the yield of such screening at this time is very low, such that the performance of these procedures may not be justified at that time. Prospective collaboration among pediatric alloHCT centers may help to provide more robust evidence-based guidelines designed to maximize utility and minimize risk.

INTRODUCTION

Over the last several decades, rates of cure for childhood leukemia have improved dramatically, with 5-year survival of acute lymphoblastic leukemia (ALL) rising from 53% in the 1970s to above 85% to 90% in the past 1 to 2 decades [1-3] and acute myelogenous leukemia (AML) survival having risen to approximately 70% today [4]. However, relapse still occurs

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in 15% to 20% of patients with ALL and 30% of AML patients, remaining the leading cause of treatment failure for these diseases. Advances in the field of allogeneic hematopoietic cell transplantation (alloHCT) have resulted in improved survival rates in relapsed leukemia (ranging from 50% to 60% in ALL today). More accurate identification of high-risk subgroups for alloHCT and improvements in transplant-related mortality contribute to improved outcomes in relapsed childhood leukemia [5]. However, despite the high prevalence and mortality of relapsed childhood leukemia, no guidelines exist regarding appropriate relapse surveillance in these patients after alloHCT.

No published prospective or retrospective studies investigated the optimal frequency or timing of routine surveillance with either bone marrow (BM) or cerebrospinal fluid (CSF) analyses in children after alloHCT. As a result, patients may be undergoing unnecessary, harmful procedures or, conversely, experiencing delayed diagnosis of relapse, potentially jeopardizing their chance for cure.

Based on anecdotal experience, we suspected that use of these measures would be physician-dependent and variable across centers. This study was designed both to characterize the existing practice nationwide and to gain some preliminary insight into the utility of post-alloHCT surveillance based on data from our center.

METHODS

This study included a nationwide survey of pediatric BM transplantation physicians and a retrospective review of data at our center. The Columbia University Institutional Review Board approved this study.

National Survey

We sent a 14-question e-mail survey (Figure 1) via Surveymonkey to 152 pediatric BM transplant physicians nationwide, identified from the Children's Oncology Group members' roster. The survey prompted respondents for information regarding their utilization of BM and CSF analysis as routine surveillance tools after alloHCT in pediatric patients with ALL and AML. The survey was conducted anonymously, and therefore specific center data were not requested of respondents. Data were collected and analyzed using Surveymonkey (New York, NY) and Microsoft Excel (New York, NY).

Single-Center Review

Patients included in this retrospective analysis were all children, adolescents, and young adults who underwent alloHCT for leukemia (ALL, AML) at New York-Presbyterian Morgan Stanley Children's Hospital between 2000 and 2012. Baseline data collected included disease, sex, age, and time to relapse. Surveillance data were collected as well, at approximately days 100, 180, 270, and 365, as per our institutional protocol. These data included results of BM biopsy, aspirate, and flow cytometry; CSF results; complete blood count;

Survey Questions:

1. How many pediatric allogeneic hematopoietic cell transplants (AlloHCT) are performed at your center/year?
2. Do you perform routine bone marrow analyses after AlloHCT in all patients with acute lymphoblastic leukemia (ALL) who are not enrolled on a research study?
3. If you perform routine post-AlloHCT bone marrow analyses in patients with ALL who are not enrolled in a research study, what is the preferred schedule?
4. Do you perform routine bone marrow analyses after AlloHCT in all patients with acute myeloid leukemia (AML) who are not enrolled on a research study?
5. If you perform routine post-AlloHCT bone marrow analyses in patients with AML who are not enrolled in a research study, what is the preferred schedule?
6. After the first year post-AlloHCT, do you perform yearly routine bone marrow analyses?
7. If yes, for how many years?
8. Do you perform routine lumbar punctures after AlloHCT in all patients with ALL?
9. If you perform routine lumbar punctures in patients with ALL, what is the preferred schedule?
10. Do you routinely administer intrathecal chemotherapy after AlloHCT in patients with ALL?
11. Do you perform routine lumbar punctures after AlloHCT in patients with AML?
12. If you perform routine lumbar punctures in patients with AML, what is the preferred schedule?
13. Do you routinely administer intrathecal chemotherapy after AlloHCT in patients with AML?
14. Would you be interested in collaborating with our group on future studies regarding routine 1-year procedures following AlloHCT?

Figure 1. Survey sent to 152 pediatric BM transplantation physicians nationwide.