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Feasibility of Treating Post-Transplantation Minimal Residual Disease in Children with Acute Leukemia

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A B S T R A C T

Outcomes are poor for patients with hematologic malignancies who experience overt relapse after allogeneic hematopoietic stem cell transplantation (HCT). Data on outcomes of post-transplantation minimal residual disease (MRD) are limited. In this single-institution, retrospective cohort analysis of children with acute leukemia and myelodysplastic syndrome, we document the pattern of relapse with a primary focus on outcomes of post-transplantation MRD. Forty of 93 patients (43%) who underwent a first allogeneic HCT and had systematic pretransplantation and post-transplantation MRD evaluations at +30, +60, +90, +180 days and +1 and +2 years post-transplantation experienced relapse. The median time to relapse was 4.8 months post-transplantation, with a median survival of 4 months post-relapse. Despite frequent, systematic, routine post-HCT disease restaging evaluation, 31 patients (78%) presented with overt disease at the time of relapse. Seven patients with acute leukemia who had post-transplantation MRD presented at a median of 1 month post-transplantation. Owing to rapid disease progression or treatment-related mortality, there was no improvement in survival in those patients whose leukemia was detected in a state of MRD post-transplantation. Our results suggest that early intervention strategies targeting post-transplantation MRD for relapse prevention in acute leukemia may not be feasible.

INTRODUCTION

Relapse is the primary cause of treatment failure in patients with hematologic malignancies who undergo allogeneic hematopoietic stem cell transplantation (HCT) [1]. Once patients have relapsed after HCT, treatment options are limited, and the outlook is generally poor [2-7]. One potential approach to improving post-transplantation outcomes involves preemptive interventions for relapse prevention. Treatment of post-transplantation minimal residual disease (MRD; defined as <5% bone marrow blasts or positive cytogenetic or molecular markers of disease) to prevent overt relapse may be one such strategy [8,9].

The majority of previous studies evaluating post-transplantation relapse in acute leukemia are based on patients presenting with overt morphological relapse or high disease burden, in whom outcomes are poor [3,4,6]. However, with frequent post-transplantation surveillance and more sensitive measures of detection, in theory disease recurrence could be detected both earlier and at a state of lower disease burden that may be more amenable to treatment, potentially leading to improved outcomes [10-12]. Certainly, preemptive immunotherapy in the setting of mixed chimerism has shown promise in relapse prevention [13-16]. In addition, treatment of MRD using donor lymphocyte infusion (DLI) in the setting of chronic myelogenous leukemia (CML) before hematologic relapse has lead to durable remissions [17-19]. Outcomes with DLI for treatment of acute leukemia are quite variable, however [20-22]. Data on the outcomes of post-transplantation MRD specifically in the setting of acute leukemia are limited [21,23-26].

In this study, we describe the presentation and management of children with hematologic malignancies who experience post-transplantation relapse. With a focus on understanding the pattern of relapse, the goal was to determine whether post-transplantation MRD is amenable to intervention for relapse prevention.

METHODS

Patients and Inclusion Criteria

This was a single-institution, retrospective cohort study of pediatric patients (age ≤21 years) who relapsed after having undergone a first allogeneic HCT for a hematologic malignancy between January 1, 2003, and December 31, 2010, at The Johns Hopkins Hospital. This cohort included all patients with a diagnosis of acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), mixed phenotypic acute leukemia (MPAL), or lymphoblastic lymphoma (LBL) irrespective of disease status, pretransplantation conditioning, donor and stem cell source, HLA matching, or any other transplant-related variables. Patients with other types of leukemia, including blast crisis CML, were excluded. For this analysis, 1 patient with LBL was analyzed with the patients with ALL. This study was approved by The Johns Hopkins Hospital's Institutional Review Board.

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Disease Monitoring, Surveillance, and Definitions

All patients underwent pretransplantation disease evaluation. Routine post-transplantation surveillance was performed at 30, 60, 90, and 180 days ± 10 days and 1 year and 2 years ± 1 month post-transplantation and as clinically indicated thereafter. Evaluation was disease-specific and included evaluation of chimerism (peripheral blood and bone marrow) and flow cytometry, cytogenetic, and molecular MRD studies (eg, *bcr/abl* in Philadelphia chromosome–positive ALL) from the bone marrow. In addition, lumbar punctures were routinely performed at the foregoing time points to assess central nervous system (CNS) status in all patients.

The day of relapse after HCT was defined as the first day of laboratory confirmation of disease presence, inclusive of post-transplantation MRD. In patients with ALL, MRD was assessed in our central reference laboratory using flow cytometry methods as described previously [27]. Following definitions published by Leung et al. [28], MRD was positive at a level ≥0.01%. For AML, the sensitivity for routine flow cytometry analysis ranged from approximately 0.1% to 1% of cells, depending on the phenotype of the initial leukemia. Treatment-related mortality (TRM) was defined as death unrelated to progressive disease and included transplantation-related mortality or death due to treatment of post-transplantation relapse.

Statistical Analysis

The primary endpoint was overall survival after post-transplantation relapse. Overall survival was defined by the date of relapse until the date of death, censored at the last follow-up date for patients who were alive at the time of this analysis. Probabilities of survival were evaluated using the Kaplan-Meier method. The cumulative incidence of relapse, adjusted for the competing risk of death from TRM, was calculated using the method of Gooley et al. [29]. The *t* test for numerical variables and Fisher's exact test for categorical variables were used to test for differences in characteristics between patients who relapsed and those who did not relapse. Analysis of variance was used to analyze the differences among the various presentations of post-transplantation relapse, specifically by the time to relapse. The level of statistical significance was set at $P < .05$. Statistical analyses were performed with Stata/IC version 12.0 (StataCorp, College Station, TX).

RESULTS

Patient and Relapse Characteristics

Forty of 93 pediatric patients (43%) who underwent a first allogeneic HCT for acute leukemia or MDS relapsed after HCT. Patient characteristics are summarized in Table 1. This number included 21 relapses among 57 patients (37%) with ALL or AML who were in morphological remission and underwent a myeloablative transplantation (Table 2). The cumulative incidence of post-HCT relapse, accounting for the competing risk of transplantation-related mortality, was 17% at 3 months, 26% at 6 months, 37% at 12 months, and 41% at 24 months (Figure 1). This included 41 patients with AML (18 of whom relapsed), 34 with ALL (16 of whom relapsed), 10 with MPAL (4 of whom relapsed), and 8 with MDS (2 of whom relapsed).

At the time of relapse, the majority of patients (n = 31; 78%) presented with morphological (>5% disease) relapse. Twenty-two patients (56%) had clinical signs and symptoms consistent with relapse, including presentation with peripheral blasts, extramedullary disease, cytopenias prompting disease evaluation, and/or other symptoms concerning for disease recurrence (eg, pain). Specifically, 3 patients had leukemia cutis or chloromatous masses, and 1 patient presented with a testicular mass that prompted further evaluation. Eight patients (21%) were asymptomatic, with relapse discovered at prespecified routine disease evaluations, including 2 patients with isolated CNS relapse. Nine patients (23%) presented with post-transplantation MRD that was detected on routine surveillance, including 7 patients with leukemia and 2 with MDS. Details regarding the presentation of relapse were not available for 1 patient with confirmed morphological relapse.

The median time to relapse for all patients was 4.8 months (range, 0.1 to 57 months) post-transplantation. There was a statistically significant difference in the time to relapse by presentation; patients with MRD-positive relapse (n = 9) presented at a median of 1 month post-HCT, those with evidence of disease detected by routine surveillance (n = 8) presented at a median of 3 months post-HCT plant, and those with overt relapse (n = 22) presented at a median of 7.5 months post-HCT ($P < .001$) (Figure 2). After patients with refractory disease were excluded, the median time to relapse for patients with AML and ALL was 4.5 months (range, 1 to 15.8 months) for patients with AML (n = 12) and 6 months (range, 1 to 29 months) for those with ALL (n = 14).

Management of Relapse

Decisions regarding the treatment of relapse varied and were based on the timing of relapse, the patient's condition, and physician and patient/family preference. Six patients received only supportive care, including hospice, palliative, or complementary medicine. In 3 patients, immunosuppressive therapy was withdrawn in response to MRD detection. Twenty-four patients received cytotoxic and/or radiation therapy, and 13 received DLI (with or without previous chemotherapy). Eleven patients were able to proceed to a second allogeneic HCT after attaining remission.

Overall Survival after Post-Transplantation Relapse and Nonrelapse Mortality

Overall survival (OS) was 30% at 6 months, 17.5% at 1 year, 15% at 2 years, and 11% at 5 years post-relapse. Median survival after relapse was 4 months (range, 0.1 to 33 months). Five of 40 patients (12.5%) are currently alive at a median follow-up of 39 months, including 2 patients who continue to be treated for active disease. One survivor had MDS and presented with MRD alone; the remaining 4 survivors presented with overt disease, including 3 with ALL and 1 with MPAL.

Death post-relapse was due to a various causes. The majority of patients died with progressive disease (n = 28). None of the 18 patients with AML survived after post-transplantation relapse. Survival did not appear to differ by therapeutic approach to relapse, with the exception of those who underwent a second HCT. The 3-year overall survival probability among the 11 patients who underwent a second transplant was 27% (95% confidence interval [CI], 6.5% to 54%), compared with 5.4% (95% CI, 0 to 20%) for those who did not ($P = .02$). The patients who proceeded to a second transplantation more often had a later relapse (median time to relapse, 8 months [range, 1 to 29 months]) than those who did not undergo a second transplantation (median time to relapse, 3.8 months [range, 1 to 58 months]). Eight patients died from TRM related to the second transplantation, including 3 patients who developed grade IV acute graft-versus-host disease (GVHD). Three patients remain long-term survivors following second transplantation.

Outcomes of Post-Transplantation MRD

All 9 patients who presented with post-transplantation MRD were discovered on routine planned surveillance. These patients presented at a median of 1-month post-transplantation (range, 1 to 6 months), with 8 exhibiting some evidence of pretransplantation disease. Among the 7 patients with leukemia, 5 had very rapid progression of disease to overt relapse, at a median of 21 days (range, 13 to 24 days) from detection of MRD despite intervention in response to MRD, including early withdrawal of immunosuppression (n = 3) and DLI (n = 2) (Table 3). All patients