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Incidence and Causes of Hospital Readmission in Pediatric Patients after Hematopoietic Cell Transplantation

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A B S T R A C T

Allogeneic (allo) and autologous (auto) hematopoietic cell transplantation (HCT) provide the potential to cure otherwise fatal diseases but they are resource-intense therapies. There is scant literature describing the burden of hospital readmission in the critical 6-month period of immunosuppression after HCT. We report the incidence, causes, and outcomes of readmission in the 6 months after day 0 of HCT and in the 30 days after hospital discharge. This study is an institutional review board–approved retrospective medical record review of children who underwent HCT at a single institution. Between January 1, 2008 and December 31, 2011, 291 children underwent HCT at our institute. Of these, 140 patients were excluded because they were not followed primarily at our institute for the first 6 months after transplantation, 14 patients were excluded because they died during their initial hospitalization, and 1 patient was excluded because the initial hospitalization was longer than 6 months. Of the remaining 136 patients, 63% had at least 1 readmission. Of the patients who underwent allo-HCT, 78% were readmitted, in contrast to 38% of auto-HCT patients ($P < .001$). For the 206 readmissions, the mean length of hospital stay was 10.7 days (range, 1 to 129). Seventy-two percent of auto-HCT patients were initially readmitted for fever, and 46% ultimately had a source identified. No risk factors for readmission were found in the auto-HCT group. Fifty-two percent of allo-HCT patients were readmitted for fever and 28% of these patients ultimately had an identified source. Gastrointestinal-related problems accounted for 30% of primary readmissions among allo-HCT patients. Patients with an unrelated donor had a trend towards increased rates of 30-day readmission ($P = .06$) and were more likely to have a second readmission ($P = .002$). Patients who were cytomegalovirus (CMV) positive before transplantation were more likely to be readmitted ($P = .02$). The majority of children who undergo HCT are readmitted during the critical 180 days after transplantation. Readmission is much more common among allo-HCT patients, in particular those with unrelated donors and CMV-positive serologies before transplantation. Fever is the most common cause of readmission in these patients, and serious infections are identified in a significant portion of patients. These findings and future research in this area will help improve both patient education and resource utilization.

BACKGROUND

Hematopoietic cell transplantation (HCT) provides potentially curative therapy for many neoplastic, hematologic, metabolic, and immunodeficiency diseases. Allogeneic HCT (allo-HCT) and autologous HCT (auto-HCT) are associated with significant risk, given the high toxicity of conditioning regimens and the prolonged period of immune suppression after transplantation. There is an extensive literature demonstrating that innate immunity, including epithelial barriers, monocytes, granulocytes, and macrophages, recover within weeks; B cell and CD8 T cell function recover over a period of months; and CD4 T cell function may take years after transplantation to normalize [1,2]. The pace of recovery varies by the type of conditioning a patient receives, donor source, and the type of cells utilized for the transplantation. After autologous transplantation, the pace of immune reconstitution would be expected to be more rapid given the lack of

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allogeneic effect and need for immunosuppressive medications, but the specific timeline has not been clearly delineated [3]. Neutropenia typically resolves in 14 to 21 days after transplantation, but there are laboratory and functional changes in the immune system for much longer [2,3]. In allogeneic transplantations, the use of peripheral blood stem cells hastens T cell reconstitution when compared with bone marrow, but the risk of infection remains high for at least 1 year after HCT [4]. When umbilical cord blood is used as the stem cell source, transplanted cells are naïve, and thus T cell–mediated cellular immunity in particular is deficient for months after transplantation [5,6]. Even as immune cell counts recover, relative immunodeficiency persists as the reconstituted T and B cell subsets likely do not hold the breadth of antigen identification seen in a normal immune system. Children receiving HCT are typically discharged soon after neutrophil engraftment—defined as an absolute neutrophil count greater than 500 cells/high power field for 3 consecutive days—but months before full immune reconstitution. Thus, there is an ongoing risk of complications and consequent readmission, which will likely vary among patient groups given the heterogeneity of the population.

Overall, 6.5% of children admitted to general children's hospitals are readmitted within 30 days of discharge, and the highest rates of readmission are in children with neoplasms [7]. Readmission rates after stem cell transplantation would be expected to be greater than that seen in general pediatric oncology patients—as high as 50% in 1 small pediatric series—yet there is a paucity of data about this population [8]. Adult and pediatric patients likely have different post-transplantation courses given the types of disease seen in adults and the burden of comorbidities; nevertheless, this population may provide insight into the pediatric HCT population. Among adult patients undergoing allo-HCT, 39% were readmitted within 30 days, most commonly for fever or infection. Receiving total body irradiation, use of an unrelated donor, and acquiring an infection during the index hospitalization were shown to be risk factors for readmission [9].

A better understanding of the incidence, causes, and risk factors for readmission in children undergoing HCT may improve quality of care and outcomes. Potential initiatives include improvement in predischarge patient education, different approaches to prophylactic antibiotics, or use of long-term central venous access. Additionally, such information would inform resource allocation and identify high-risk populations requiring close monitoring and follow-up. A study of pediatric cardiothoracic surgery patients—another group at high risk of readmission—showed that a firm understanding of the risk factors for readmission could inform quality improvement measures in the postoperative period [10].

In this study, we describe the incidence, causes, risk factors, and outcomes of hospital readmission in a large pediatric HCT program at a tertiary freestanding pediatric hospital. Readmissions were evaluated in the critical 6 months after day 0 of transplantation, during which time significant immune suppression persists. Given that the standard metric for assessing readmissions after hospitalization is 30 days from discharge, we also report 30-day readmission data. We hypothesized that the readmission rates would be higher among children undergoing allo-HCT compared with those undergoing auto-HCT, and that graft-versus-host disease (GVHD) and complications occurring during initial hospitalization may be risk factors for readmission during the 180 days after transplantation. Furthermore, we hypothesized that readmission in itself may have prognostic impact on outcomes at 1 year.

METHODS

Patients and Data Collection

This study is an institution review board–approved retrospective medical record review of 291 consecutive children who underwent HCT between January 1, 2008 and December 31, 2011 at the Dana-Farber/Boston Children's Hospital Cancer Center (Figure 1). Of these, 140 patients (75%, n = 106, allo-HCT; 25%, n = 34, auto-HCT) were excluded because they were not followed exclusively at the Dana-Farber for 6 months after discharge from the primary hospital admission (index hospitalization), and 14 patients (71%, n = 10, allo-HCT; 29%, n = 4, auto-HCT) were excluded because they died during their initial hospitalization. One allo-HCT patient was hospitalized for more than 6 months after day 0 of hospitalization and was consequently omitted from analysis. Hospital records were reviewed for the remaining 136 patients from the day of admission for HCT to 6 months after the day of transplantation. Of the 136 included patients, 65% received allo-HCT (n = 88) and 35% underwent auto-HCT (n = 48). From the index hospitalization we recorded age at transplantation, gender, underlying disease, transplantation type (auto, allo), donor relation (related, unrelated), time to neutrophil count > 500, presence of GVHD during initial hospitalization for allo-HCT patients, presence of infection (bacterial, viral, or fungal), whether there was an admission to the intensive care unit (ICU) after transplantation, and whether the patient was readmitted to our hospital within 6 months after transplantation (6-month readmission) and/or within 30 days from discharge from the index hospitalization (30-day readmission). Patients who underwent planned tandem transplantations were reported beginning from the date of the last transplantation. Planned readmissions, such as those for antibody therapy or scheduled elective surgeries, were not classified as readmissions.

All allo-HCT patients and/or donors who were IgG positive for cytomegalovirus (CMV) before HCT were screened weekly for viral reactivation by antigen testing or quantitative PCR.

In our practice, criteria for discharge after HCT include the following: (1) neutrophil engraftment, (2) no active infections, and (3) no active GVHD. The majority of patients are discharged with a central line. Before discharge, all patients and their families undergo a formalized discharge teaching session with a dedicated clinical nurse specialist, which includes discussion of readmission criteria (fever, diarrhea, cough, etc). In addition, all patients have nutrition consultation during HCT and at the time of discharge.

For those patients readmitted, additional information was collected, including the number of readmissions within 6 months from the day of transplantation (day 0), the cause of readmission, the length of readmission, transfer to the ICU during readmission, and documented infection during readmission.

For all patients, 100-day, 6-month, and 1-year overall mortality, transplantation-related mortality (TRM) data, and survival data were collected.

Statistical Analysis

The readmission rate was calculated by taking the total number of patients with at least 1 readmission in the given time period and dividing by the 136 patients reviewed; a 95% confidence interval (CI) was placed on this rate. Risk factors for readmission, including age, positive blood culture, transplantation type, donor type, and GVHD at time of discharge, were analyzed with univariate Fisher's exact test and a multivariate logistic regression model. To assess the impact of readmission on mortality, Kaplan-Meier curves of overall survival (OS), were plotted for all patients, by readmission versus no readmission, and a log-rank test comparison of the curves was performed. OS point estimates are at 1 year ± standard error. OS was calculated starting from the time of transplantation until death from any cause or until last contact if the patient did not die. A logistic regression model was used to test if readmission was associated with 1-year mortality. Logistic regression models were used to assess the prognostic impact of age, positive blood culture during readmission, and transplantation type on second readmission, and Cox proportional hazard regression models assessed the effect of these factors on time to second readmission. The same methods were used to address the impact of peak fever at readmission, positive blood culture during readmission, age and donor type on second readmission, and time to second readmission. Cumulative incidence of TRM, with adjustment for death from other causes, was calculated according to the methods of Kalbfleish and Prentice [11].

RESULTS

Readmission Rates

For the 136 patients in our study, 41% (n = 56) were readmitted within 30 days of discharge from their primary transplantation hospitalization; 52% (n = 46) of allo-HCT patients and 21% of auto-HCT patients (n = 10) ($P < .01$). In