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Risk Factors for Readmission after Allogeneic Hematopoietic Stem Cell Transplantation and Impact on Overall Survival

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Patients treated with allogeneic hematopoietic stem cell transplantation (HSCT) are presumed to be at high risk for hospital readmission. The objective of this study was to identify the incidence and associated risk factors for readmissions in allogeneic HSCT patients and to evaluate the effect of readmissions on overall survival. In this retrospective review, we included 1141 HSCT patients (503 patients receiving a myeloablative [MAC] HSCT and 638 a reduced-intensity conditioning [RIC] HSCT). We measured rates of readmission at 30 days after discharge from HSCT and by day +100 after HSCT. Reasons for readmission, risk factors for readmission, and effect on overall survival were assessed. In the MAC group, 130 of 459 (28.3%) patients were readmitted within 30 days of discharge and 195 of 456 (42.8%) patients by day 100. In the RIC group, 105 of 600 (17.5%) patients were readmitted within 30 days of discharge and 185 of 595 (31.1%) patients by day 100. There were significantly more readmissions in the MAC group at both the 30-day ($P < .001$) and day +100 time points ($P < .001$). The most frequent reason for readmission was infection (28.2% in MAC group, 27.3% in RIC group). The occurrence of infection during the index admission was the only risk factor significant in both groups at both time points in the multivariable regression analysis. Readmission was significantly associated with decreased overall survival in both groups and at both time points. MAC patients are readmitted significantly more than RIC patients. Infection is the most common cause of readmission after HSCT and the occurrence of infection during the index transplantation admission is a significant risk factor for readmission. Readmission within 30 days of discharge and by day +100 after transplantation was a significant risk factor for a lower 5-year overall survival rate in both groups.

INTRODUCTION

Hospital readmissions shortly after index hospitalization increases health care costs. Recent studies suggest that approximately 20% or greater of Medicare patients are readmitted within 30 days of discharge, with the vast majority of these readmissions being unplanned [1-3]. Much of the earlier research on 30-day readmissions in the United States focused on pneumonia, heart failure, and acute myocardial infarction, with studies demonstrating marked heterogeneity in readmission rates across the country [4-7]. There is also evidence that readmission rates vary by race and site of care [8]. Readmissions are felt to be an indicator of failure of care transition. They are also costly, with Medicare spending an estimated 17 billion dollars annually on readmissions within 30 days of discharge [1]. Likewise, 30-day readmissions have become an important quality metric in health care and the Affordable Care Act has enacted the Hospital Readmissions Reduction Program [9]. Although current measures exclude oncology patients, the program will likely continue to expand to include these patients in the future. This potentially has significant implications for oncology, as very little is known about the readmission profiles of cancer patients. Gaining a better understanding of the risk factors for readmissions among the oncology population has the potential to result in substantial health care cost savings as well as enhance quality of life for oncology patients.

Hematopoietic stem cell transplantation (HSCT) readmission rates are especially poorly described. Although HSCT is potentially curative for patients with otherwise incurable hematologic malignancies, the procedure is associated with significant post-transplantation morbidity and mortality. HSCT results in defects in innate and adaptive immunity that increase the risk of opportunistic infections. Moreover, there is an intrinsic risk of graft-versus-host disease (GVHD) and relapse. These vulnerabilities increase the risk of readmission

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in the weeks to months after HSCT. The timing of these vulnerabilities is often affected by the type of conditioning regimen used. Myeloablative conditioning (MAC) regimens cause irreversible cytopenias. Nonmyeloablative (NMA) conditioning regimens cause minimal cytopenias. Reduced-intensity conditioning (RIC), an approach that has become more common over the years, features cytopenias of variable duration.

Although HSCT is a relatively uncommon procedure in general, a 2009 Agency for Healthcare Research and Quality report noted that it was among the top 10 procedures with the greatest increase in hospital costs from 2004 to 2007, with a growth rate of 84.9% from $694 million to $1.3 billion, related to both costs and the number of hospitalizations [10]. There has been a significant increase in the number of transplantations performed both domestically and worldwide over the past several years [11]. Transplantation rates are expected to continue to increase with anticipated improvements in transplantation technology and supportive care practices, in addition to the emergence of new indications and alternative graft sources [12,13]. Given the high-risk nature of these immunocompromised patients, the threshold to readmit is relatively lower and many quality metrics cannot be easily generalized to this population. The purpose of our study was to identify the incidence of and reasons for readmission in transplantation patients, as well as to explore associated risk factors for readmission and the impact of readmission on overall survival (OS).

METHODS

Patients and Setting

A retrospective review of patients receiving MAC, RIC, or NMA conditioning HSCT at Dana Farber/Brigham and Women's Hospital between January 1, 2005 and December 31, 2010 was performed. For the purpose of this analysis, all patients receiving an NMA conditioning regimen were analyzed as part of the RIC group. Conditioning regimen intensity was defined according to Center for International Blood and Marrow Transplant Research criteria [14]. Medical records of 1141 HSCT patients were reviewed, with 503 patients receiving a MAC transplant and 638 patients receiving a RIC transplant. The most common MAC regimen used was cyclophosphamide with total body irradiation (88% of patients) and the most common RIC regimen used was fludarabine/busulfan (89% of patients). Recipients of cord blood units and patients who previously received an allogeneic transplant were excluded before the analysis. All patients received their stem cells while admitted to an inpatient bone marrow transplantation unit. Per institutional guidelines, the RIC transplantation patients were discharged on day +1 to 2, unless complications occurred. The MAC transplantation patients remained hospitalized until their absolute neutrophil count recovered above 500 cells/uL for 2 days, they were afebrile, and they were able to manage independently at home. All patients received discharge medication teaching from an oncology pharmacist, registered nurse, or oncology-trained physician assistant and discharge precautions teaching from an oncology registered nurse. Follow-up appointments were arranged by the inpatient team for within 5 days of discharge.

Measurements

The 30-day after discharge and the day 100 after transplantation, a key time point in transplantation, readmission rates were examined. Information on hospital readmissions was collected retrospectively from the physician documentation in the electronic chart, including readmissions outside of the home institution when available. We analyzed age, gender, race, ethnicity, marital status, distance traveled, median income for home zip code, insurance type, primary caregiver, disease type, disease risk index [15], prior treatment with radiation therapy, prior autologous transplantation (for RIC only), disease status at time of transplantation, donor type, stem cell product type, use of total body irradiation during conditioning (for MAC only), documented infection during index HSCT admission, grade II to IV GVHD [16] during index HSCT admission, hepatic veno-occlusive disease (for MAC only) during index HSCT admission, and length of stay for index HSCT admission. Myeloid malignancies included acute myelogenous leukemia, myelodysplastic syndromes, myeloproliferative neoplasms, and chronic myelogenous leukemia. Lymphoid malignancies included acute lymphoblastic leukemia, biphenotypic leukemia, lymphomas, multiple myeloma, and plasma cell leukemia. Other conditions included aplastic anemia and other benign hematologic disorders. Infections were defined as any documented bacterial, viral, or fungal infections with isolation of a specific microorganism. The only exception was pneumonia, for which the presence of both clinical and radiologic findings of pneumonia was accepted as an infection.

Statistical Analysis

To identify the risk factors for 30-day or day +100 readmission rates, patients who died during their index transplantation admission or before the corresponding time points without readmission were excluded (44 in MAC group, 38 in RIC group). An additional 2 patients who stayed in the hospital for more than 100 days during their transplantation admission were also excluded from the day +100 readmission analysis. Potential risk factors were compared between patients readmitted and those not admitted using the Fisher's exact test or the Wilcoxon rank-sum test [17,18]. Factors with a univariate *P* value less than or equal to .20 were further evaluated in the multivariable logistic model. To evaluate the impact of 30-day or day +100 readmission on survival, a landmark analysis was performed among the patients who survived beyond the corresponding time points. Survival curves were estimated using the Kaplan-Meier method and were tested between groups using the log-rank test [19,20]. The effect of readmission on OS was also evaluated in a Cox regression model after adjusting for age, donor type, and the disease risk index [21].

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RESULTS

In the MAC group, 130 of 459 (28.3%) patients were readmitted within 30 days of discharge and 195 of 456 (42.8%) patients were readmitted by day 100 after transplantation. In the RIC group, 105 of 600 (17.5%) patients were readmitted within 30 days of discharge and 185 of 595 (31.1%) patients were readmitted by day 100 after transplantation. As shown in Table 1, there were significantly more readmissions in the MAC group at both the 30-day ($P < .001$) and day +100 time points ($P < .001$).

Taking into account all readmissions, in both groups the most frequent reasons for readmission were infection (28.2% in MAC group, 27.3% in RIC group), fever without a source (19.2% in MAC group, 19.9% in RIC group), and GVHD (18.0% in MAC group, 15.9% in RIC group). Other less common reasons included veno-occlusive disease, gastrointestinal diagnoses, acute kidney injury, and neurologic diagnoses. Of the 34 RIC patients with an initial readmission reason of fever without a source at the 30-day readmission time point, 15 of the patients (44%) were neutropenic at the time of readmission. Baseline characteristics with univariate analysis of both the readmitted and the not-readmitted subsets for the MAC and RIC groups at each readmission time point of interest are summarized in Tables 2 and 3, respectively, and are further discussed below. Results of the multivariate logistic regression model of risk factors for each group and time point are summarized in Table 4 and are further discussed below.

MAC: 30-Day Readmission Risk Factors

Compared with those in the MAC group who was not readmitted by 30 days after discharge, the readmitted group

Table 1
Readmission Rates

Conditioning	30-Day Readmission Rate	Day +100 Readmission Rate
MAC	130 of 459 (28.3%)	195 of 456 (42.8%)
RIC	105 of 600 (17.5%)	185 of 595 (31.1%)
P Value	<.001	<.001