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Readmissions after Umbilical Cord Blood Transplantation and Impact on Overall Survival

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Patients treated with allogeneic hematopoietic stem cell transplantation (SCT) have high rates of readmission, but the incidence after umbilical cord blood transplantation (UCBT) is poorly described. The goal of this study was to identify the incidence and risk factors for readmission after UCBT and the impact of readmission on overall survival (OS). A retrospective review of patients receiving a UCBT at Dana-Farber/Brigham and Women's Hospital between January 1, 2004 and December 31, 2013 was performed. The readmission rates 30 days after discharge from the UCBT admission and at day +100 after the UCBT were examined. Reasons for readmission, as well as sociodemographic, disease-, and SCT-related variables were evaluated. Predictors of readmission and the impact of readmission on OS were identified using multivariate regression analysis. Of patients who received a UCBT, 42 of 126 patients (33.3%) were readmitted within 30 days of discharge and 57 of 123 patients (46.3%) were readmitted by day +100 after transplantation. The most common causes for readmission were infection (38.3%), fever without a source (14.8%), and graft-versus-host disease (8.6%). Infection during the index admission was the only significant risk factor for readmission at both time points in a univariate and multivariate regression analysis (OR, 11.66; 95% CI, 2.77 to 49.13; $P < .01$ and OR, 5.4; 96% CI, 1.87 to 15.58; $P < .01$). Prior radiation therapy was also associated with an increased risk of readmission at both time points in the multivariate regression model (OR, 20.6; 95% CI, 3.53 to 120.04; $P \leq .01$ and OR, 5; 95% CI, 1.21 to 20.71; $P = .03$). The multivariate regression model also showed that black race and a median income of <60,000 in the patient's home zip code increased the risk of readmission by day +100 (OR, 30.17; 95% CI, 1.33 to 684.48; $P = .03$ and OR, 2.88; 95% CI, 1.04 to 7.8; $P = .04$, respectively). After adjusting for age, disease type, and the disease status at transplant, OS was reduced for the patients who were readmitted by day +100 (HR, 2.44; 95% CI, 1.46 to 4.06; $P < .01$). There was also a trend toward decreased survival in patients readmitted 30 days after discharge (HR, 1.58; 95% CI, .96 to 2.6; $P = .07$). Readmissions are common after UCBT. Infections and fever without a source are the most common causes of readmission. Being readmitted by day +100 resulted in a lower 5-year OS rate as compared with patients who were not readmitted. Prior radiation and infection during the transplant admission resulted in increased risk of readmission by 30 days and day +100. Similarly, race and socioeconomic status predicted readmission by day +100. Further understanding of the mechanisms leading to readmissions in these groups may allow for identification of interventions that could reduce readmissions and thus improve mortality.

INTRODUCTION

In recent years, readmission rates have been used as a tool to assess quality of care [1]. Early studies investigated rates and causes of 30-day readmissions for patients with pneumonia, heart failure, and myocardial infarction [2-5]. Causes of avoidable readmissions have included hospital-acquired infections and other complications, failure to reconcile medications, poor communication, and inadequate transitions in care [6]. Readmission rates were also found to vary by race and location of care [7].

Readmissions also add significantly to healthcare costs. According to a study in 2009, nearly 20% of Medicare beneficiaries were readmitted within 30 days after discharge with an annual cost of approximately 17 billion dollars [8]. These findings have had important implications for healthcare policy. The Hospital Readmissions Reduction Program, established by the Centers for Medicare & Medicaid Services, was

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designed to penalize hospitals up to 3% of their Medicare reimbursement when a substantial proportion of their patients were readmitted within 30 days of discharge [9]. Although oncology patients have been excluded from these assessments, readmission rates may similarly serve as a marker of quality for this patient population. Further understanding of the rates and causes of readmissions will potentially lead to improvement in care and reduction in healthcare costs for patients with cancer.

Although hematopoietic stem cell transplantations (HSCTs) offer a potentially curative option for patients with hematologic malignancies and bone marrow failure, they are associated with significant degree of morbidity and mortality and high rates of hospital readmissions [10,11]. In a previous study from our institution, the 30-day readmission rate after myeloablative conditioning regimens was 28.3% and after reduced-intensity conditioning (RIC) regimens, 17.5% [10]. The readmission rate by day +100 was 42.8% for myeloablative conditioning regimens and 31.1% for reduced-intensity conditioning regimens [10]. Infections were the most common cause for readmission and an independent risk factor for readmission. Readmissions were also found to be associated with reductions in mortality. Similar studies have demonstrated comparable results [11,12].

In the absence of an HLA-matched donor, patients may have the option of an umbilical cord blood transplant (UCBT) [13]. Although UCBTs result in similar leukemia-free survival as compared with matched related donor or matched unrelated donor transplants, little is known about rates or causes of readmissions in these patients [14,15]. The purpose of this study was to identify the incidence and risk factors for readmission after UCBT as well as the impact of readmission on overall survival (OS).

METHODS

Patients and Setting

A retrospective review of patients receiving a UCBT at Dana Farber/Brigham and Women's Hospital between January 1, 2004 and December 31, 2013 was performed. The medical records of 144 UCBT patients were reviewed. Patients received myeloablative conditioning regimens. The most commonly used regimen was fludarabine, melphalan, and antithymocyte globulin. All patients received their stem cells while admitted to an inpatient stem cell transplant unit. Patients remained hospitalized until their absolute neutrophil count recovered above 500 cells/μL for 2 days and until they were afebrile and able to manage independently at home. All patients received discharge medication teaching from an oncology pharmacist, registered nurse, or oncology-trained physician assistant. Patients also received discharge precautions teaching from an oncology registered nurse.

Follow-up appointments were arranged by the inpatient team. Patients were seen by a registered nurse and a nurse practitioner or physician's assistant within 5 days of discharge for possible transfusions or hydration and by a transplant oncologist within 7 days. Patients were subsequently seen twice weekly for the first month from discharge and then weekly, although this varied depending on clinical status. Most patients who lived greater than 1.5 hours from the hospital resided in a local hotel for at least 2 weeks after discharge. These patients were also seen on a biweekly basis for the first month and therefore required reliable transportation.

At the time of this study, all patients needed to follow up at our transplant center. Our center is now partnering with local oncologists to share care post-transplant to decrease patient hardship. All patients with fevers or symptoms concerning for infection were readmitted for parenteral antibiotics with an antipseudomonal agent.

Measurements

The readmission rates 30 days after discharge from the transplant admission and at day 100 after the transplant, a key time point in transplant medicine, were examined. Information on hospital readmissions was collected retrospectively from physician documentation in the electronic chart. This included information outside of the home institution when available. We analyzed age, gender, race, ethnicity, marital status, distance traveled, median income for the patient's home zip code, insurance type, primary caregiver, disease type, treatment with radiation therapy before the transplant admission, prior autologous transplant, disease status at time of transplant, documented infection during index HSCT admission, grades II to IV graft-versus-host disease during index HSCT admission, and hepatic veno-occlusive disease during index HSCT admission. Myeloid malignancies included acute myelogenous leukemias, 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 benign hematologic conditions. 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

Patients who died during their transplant admission or who died before 30 days from discharge or day +100 were excluded. Eighteen and 20 patients were excluded from the 30-day and day +100 analysis, respectively. An additional 1 patient who stayed in the hospital for more than 100 days during his or her transplant admission was also excluded from the day +100 readmission analysis. Patient characteristics were compared between patients readmitted and those not admitted using the Fisher's exact test or the Wilcoxon rank sum test [16,17]. Potential risk factors were evaluated in multivariable logistic models. 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 [18,19]. The effect of readmission on OS was also evaluated in a Cox regression model after adjusting for age, disease type, and the disease status at transplant [20].

RESULTS

Of patients who received a UCBT, 42 of 126 patients (33.3%) were readmitted within 30 days of discharge and 57 of 123 patients (46.3%) were readmitted by day +100 after transplantation. The most common causes for readmission were infection (38.3%), fever without a source (14.8%), and graft-versus-host disease (8.6%). Examples of infections included bacteremia, pneumonia, invasive aspergillosis, adenovirus, BK virus, human herpes virus 6, cytomegalovirus, and *Clostridium difficile*. Most patients classified as fever without a source were not neutropenic but were empirically treated with antibiotics until culture data returned. Other less common reasons for admission included gastrointestinal complaints, acute kidney injury, relapse of malignancy, neurologic diagnoses such as headaches or altered mental status, and hepatic veno-occlusive disease (Table 1).

Thirty-Day and Day +100 Readmission Risk Factors

Compared with patients who were not readmitted within 30 days of discharge, readmitted patients were more likely

Table 1
Reasons for Readmission

Reason	Percent (n)
Infection	38.3 (31)
Fever without a source	14.8 (12)
GVHD	8.6 (7)
GI	7.4 (6)
AKI	6.2 (5)
Relapse	6.2 (5)
Other, not otherwise specified	6.2 (5)
Multiple	4.9 (4)
Neurologic diagnosis	4.9 (4)
VOD	2.5 (2)

Infection indicates any infection where an organism was identified. Fever without a source indicates a fever where no infectious cause was identified. GI indicates gastrointestinal diagnoses without an identified infectious source or GVHD.
GVHD indicates graft-versus-host disease; GI, gastrointestinal; AKI, acute kidney injury; VOD, veno-occlusive disease.