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Infection Rates among Acute Leukemia Patients Receiving Alternative Donor Hematopoietic Cell Transplantation

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A B S T R A C T

Alternative graft sources (umbilical cord blood [UCB], matched unrelated donors [MUD], or mismatched unrelated donors [MMUD]) enable patients without a matched sibling donor to receive potentially curative hematopoietic cell transplantation (HCT). Retrospective studies demonstrate comparable outcomes among different graft sources. However, the risk and types of infections have not been compared among graft sources. Such information may influence the choice of a particular graft source. We compared the incidence of bacterial, viral, and fungal infections in 1781 adults with acute leukemia who received alternative donor HCT (UCB, n= 568; MUD, n = 930; MMUD, n = 283) between 2008 and 2011. The incidences of bacterial infection at 1 year were 72%, 59%, and 65% ($P < .0001$) for UCB, MUD, and MMUD, respectively. Incidences of viral infection at 1 year were 68%, 45%, and 53% ($P < .0001$) for UCB, MUD, and MMUD, respectively. In multivariable analysis, bacterial, fungal, and viral infections were more common after either UCB or MMUD than after MUD ($P < .0001$). Bacterial and viral but not fungal infections were more common after UCB than MMUD ($P = .0009$ and <.0001, respectively). The presence of viral infection was not associated with an increased mortality. Overall survival (OS) was comparable among UCB and MMUD patients with Karnofsky performance status (KPS) ≥ 90% but was inferior for UCB for patients with KPS < 90%. Bacterial and fungal infections were associated with poorer OS. Future strategies focusing on infection prevention and treatment are indicated to improve HCT outcomes.

INTRODUCTION

Umbilical cord blood (UCB) is an important hematopoietic cell source for patients without matched related (MRD) or matched unrelated donors (MUD). Several studies have shown comparable survival after hematopoietic cell transplantation (HCT) using either MUD, mismatched unrelated (MMUD) donors, or UCB transplantation (UCBT) [1-3]. In general, engraftment is delayed in UCBT, but the incidence of chronic graft-versus-host disease (GVHD) is lower. To overcome a low cell dose in UCBT, multiple investigators have used double UCBT in adults after either myeloablative (MA) or reduced-intensity conditioning (RIC) regimens [4-7]. Despite these advances, poor immune reconstitution remains a significant problem after UCBT [8].

Several studies have reported a high rate of viral infection after UCBT. The incidence of human herpes virus-6 infection ranges from 0 to 10% after MUD HCT and from 5% to 21% after UCBT [9]. High viral infection risk after UCBT is likely related to the delayed immune reconstitution after transplantation [10-13]. Fungal infections remain an important cause of morbidity and mortality after allogeneic HCT, particularly with alternative donor HCT. The incidence of invasive fungal infection has been reported at 9% after allogeneic HCT; some studies show an increase in fungal infection with MUD compared with MRD transplantations [14-16]. In a study of 1400 patients in China, mortality was over 30% in patients with proven invasive fungal infection [15]. Bacterial infections, especially after UCBT, are associated with high mortality. In 241 patients undergoing single UCBT, the incidence of bloodstream bacterial infection was 52% with a 12% mortality rate [17].

The incidence, type, and risk factors for infection have not been formally compared in a large data set among MUD, MMUD, and UCBT. In this study, we seek to compare the incidence and type (fungal, viral, bacterial) of infections among transplantation patients with acute leukemia who received UCB, MUD, and MMUD HCT. As infections are a significant cause of morbidity, mortality, and resource utilization after HCT, data from this study may enable transplantation physicians to better select the optimal donor source and to use more effective infection prevention and treatment strategies.

PATIENTS AND METHODS

Transplantation Registry

Data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR), a research affiliate of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program established in 2004. It comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute data on consecutive allogeneic and autologous HCT procedures to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program coordinating center in Minneapolis. Participating centers report longitudinal data on all transplantations and compliance is monitored by on-site audits. Transplantation essential data, collected for consented patients participating in CIBMTR data collection, include demographic, disease type and stage, survival, relapse, graft type, the presence of GVHD, and cause of death data. A subset of CIBMTR participants are selected for comprehensive research level data collection by weighted randomization. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule. Studies conducted by the CIBMTR are performed under guidance and review of the institutional review board of the National Marrow Donor Program.

Patients

The study population consists of patients ≥16 years old with acute leukemia in first or second complete remission (CR) receiving a transplant with a single or double unrelated UCBT, a MUD, or a single antigen/allele MMUD who were reported to the CIBMTR between 2008 and 2011. First HCTs, receiving either MA or nonmyeloablative (NMA)/RIC regimens were included. Patients receiving ex vivo T cell depletion, CD34 selection, or post-transplantation cyclophosphamide were excluded. Because of the small sample size, patients receiving haploidentical HCT were excluded.

Infection Data

Infections are reported to the CIBMTR using an organism code and site code. There are no data provided to assess infection prophylaxis, treatment, diagnostic criteria utilized by the center, or severity. Centers are instructed to report clinically significant infections with both on-line and in-person education regarding appropriate reporting. Data are reviewed by clinicians to assess appropriateness for inclusion in analyses. For yeast infections, sites were limited to lower respiratory infections, blood stream infections, and visceral organ involvement. Other fungal infections were included as reported by the center. Viral data excluded from analysis were suspected or "other virus" infection in the lips, nasopharynx/upper airway, feces, or skin. Bacterial data excluded were suspected bacterial infection in the oral cavity, lips, feces, nasopharynx/upper airway, and skin; *H. pylori*; vancomycin-resistant *Enterococcus* in the gastrointestinal tract not specified, feces, genital area, skin not specified; *E. coli* or "other bacteria" in the genital tract; coagulase-negative *Staphylococcus* in the oral cavity, nasopharynx/upper airway, genitourinary tract not specified, or skin not specified; *Enterococcus* spp., *Pseudomonas* spp., or *Streptococcus* spp. in feces; and *Streptococcus* or *Corynebacterium* (non-diphtheroids) species on the skin.

Outcomes and Study Definitions

The primary objective of this study was to compare the incidences of bacterial, fungal, and viral infections at 100 days and 1 year after transplantation for alternative donor HCT. To account for multiple infectious episodes occurring in a single patient and adjusted for a period of time at