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Reduced-Intensity Conditioning Stem Cell Transplantation: Comparison of Double Umbilical Cord Blood and Unrelated Donor Grafts

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There are little data comparing umbilical cord blood (UBC) and conventional stem cell sources for reduced-intensity conditioning (RIC) hematopoietic stem cell transplantation (HSCT). We performed a retrospective analysis of RIC HCST using double UCB (dUCB) grafts and RIC HSCT using unrelated donor (URD) grafts. The study included 64 dUCB transplantations and 221 URD transplantations performed at Dana-Farber Cancer Institute and Massachusetts General Hospital between 2004 and 2008. The cumulative incidence of grade II-IV acute graft-versus-host disease (GVHD) was 14.1% for dUCB and 20.3% for URD ($P = .32$). The 2-year cumulative incidence of chronic GVHD was significantly lower in dUCB compared with URD (21.9% versus 53.9%; $P < .0001$). The 2-year cumulative incidence of nonrelapse mortality was significantly higher in dUCB (26.9% versus 10.4%; $P = .0009$). In our analysis, dUCB HSCT and URD HSCT had comparable 3-year overall survival (46% in dUCB and 50% in URD; $P = .49$) and progression-free survival (30% in dUCB and 40% in URD; $P = .47$). dUCBT was associated with greater nonrelapse mortality despite less chronic GVHD. Our findings suggest that the use of 2 partially matched UCB units appears to be a suitable alternative for patients undergoing RIC HSCT without an HLA-matched donor.

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INTRODUCTION

In the last decade, umbilical cord blood (UCB) has emerged as a viable stem cell source for allogeneic hematopoietic stem cell transplantation (HSCT) in adult patients who lack a well-matched related or unrelated adult donor [1]. With increasing experience and advances in supportive care, outcomes after UCB transplantation (UCBT) have improved [2]. In the setting of myeloablative conditioning regimens, 2 recent large retrospective analyses showed comparable outcomes in UCBT and adult unrelated donor (URD) peripheral blood stem cell (PBSC) or bone marrow (BM) transplantation for adult patients with hematologic malignancies [3,4].

In related and unrelated PBSC transplantation, reduced-intensity conditioning (RIC) regimens achieve reliably high rates of engraftment with acceptable toxicity. RIC regimens thus make allogeneic hematopoietic stem cell transplantation (HSCT) feasible for patients previously considered ineligible because of older age or medical comorbidities. A concern with RIC regimens in UCBT has been that insufficient conditioning intensity might not allow reliable engraftment, particularly in UCBT, in which hematopoietic progenitor cell numbers are lower relative to HSCT with adult stem cell sources. The advent of new strategies such as the use of 2 partially matched UCB units (ie, double UCBT [dUCBT]) and ongoing development of in vitro UCB stem cell expansion, along with the publication of several series of successful RIC UCBT [5-8] have promoted the increased adoption of RIC regimens in UCBT.

To date, there have been no published studies comparing outcomes between UCBT and unrelated donor HSCT after RIC. We undertook a retrospective

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analysis at our institutions comparing patients with advanced hematologic malignancies undergoing RIC HSCT using stem cells from UCB and patients undergoing RIC HSCT using stem cells from adult unrelated donors.

METHODS

Patients and Supportive Care

All patients undergoing RIC HSCT using either UCB stem cells or stem cells from well-matched unrelated adult donors between January 1, 2004, and December 30, 2008, at Dana-Farber/Brigham and Women's Cancer Center and Massachusetts General Hospital Cancer Center were included. These centers share UCBT clinical protocols and work under a common Institutional Review Board. For patients who underwent more than one RIC HSCT, only the first transplantation was considered in this analysis. The choice to use RIC was based on the physician's judgment, the underlying disease, disease status, and the patient's age and comorbidities. In general, at our institutions, RIC regimens are recommended for patients age >60 years when using URD stem cells and patients age >30 years when using UCB. UCB units for all of the 64 patients receiving RIC dUCBT were at least 4/6 HLA matched (allele-level typing at HLA-A, -B, and -DRB1) with each other and with the recipient. Each UCB unit had at least 1.5×10^7 total nucleated cells/kg recipient weight, with the sum of the 2 units at least 3.7×10^7 total nucleated cells/kg. URD grafts were 7/8 or 8/8 HLA allele-level matched (HLA-A, -B, -C, and -DRB1). Eligibility for transplantation, conditioning regimens, and supportive care were similar in the 2 centers and included inpatient hospitalization in single hospital rooms with high-efficiency particulate air filtration. Antiviral prophylaxis against herpes simplex/varicella zoster virus and *Pneumocystis jirovecii* prophylaxis was continued for at least 1 year after HSCT. Cytomegalovirus was monitored routinely after HSCT and treated preemptively. In patients who underwent dUCBT, Epstein-Barr virus (EBV) and human herpesvirus 6 also were monitored routinely. All patients provided consent for use of protected health data for research as approved by our Institutional Review Board.

Engraftment and Graft-versus-Host Disease

Neutrophil engraftment was defined as an absolute neutrophil count (ANC) >500/μL on 3 consecutive measurements. Platelet recovery was defined as 2 consecutive measurements of >20,000/μL unsupported. Graft-versus-host disease (GVHD) prophylaxis regimens are described below. Tapering of immune suppression was initiated at 2-4 months after transplantation, with the goal of cessation by approximately 6 months in the absence of GVHD. No preemptive or planned prophylactic donor lymphocyte infusions (DLI) were given. Acute GVHD was graded using consensus grading criteria [9], and cumulative incidence was calculated through day 200 post-HSCT, given that acute GVHD often presents after day 100 in patients undergoing RIC HSCT. Chronic GVHD was defined clinically by the treating physicians; grading of the severity of chronic GVHD was not included in this analysis because of the recent changes in the classification scheme [10].

Chimerism Analysis

Total donor chimerism was assessed from peripheral blood samples at approximately day +30 (range, day +20 to day +50) and day +100 (range, day +90 to day +120) after HSCT. Chimerism was not routinely analyzed from BM samples. Genotyping was determined by short tandem repeat typing using the ABI Profiler Plus Kit and ABI 310 Genetic Analyzer (Applied Biosystems, Bedford, MA). "Informative" alleles specific to the donor or recipient were used for chimerism determination.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. The Wilcoxon rank sum test, χ^2 test, or Fisher exact test was used for 2-sample comparisons. Cumulative incidence curves for GVHD were constructed, reflecting death or relapse without development of GVHD as a competing risk. Cumulative incidence curves for relapse and nonrelapse mortality (NRM) were constructed, reflecting time to relapse and time to nonrelapse death as competing risks. The difference between cumulative incidence curves in the presence of a competing risk was tested using the method of Gray [11]. Time to relapse and time to nonrelapse death were measured from the date of stem cell infusion.

Overall survival (OS) and progression-free survival (PFS) were calculated by the Kaplan-Meier method. OS was defined as the time from stem cell infusion to death from any cause; PFS, as the time from stem cell infusion to relapse, disease progression, or death from any cause. The log-rank test was used to compare Kaplan-Meier curves.

Potential prognostic factors for OS, PFS, relapse, and NRM were examined in a Cox proportional hazards model and a competing-risks regression model [12]. Variables examined in the multivariate models included stem cell source (dUCB versus URD), age (≥50 years versus <50 years), patient–donor sex mismatch (M→F versus other), previous autologous stem cell transplantation, disease risk status, disease (myeloid versus lymphoid), GVHD prophylaxis regimen (sirolimus versus no sirolimus), and year of HSCT.