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Brief Articles

Unrelated Cord Blood Transplantation for Patients with Primary or Secondary Myelofibrosis

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A B S T R A C T

To determine whether umbilical cord blood transplantation (UCBT) is an alternative cure for myelofibrosis (MF), we evaluated 35 UCBTs reported to Eurocord. Seven patients had secondary acute myeloid leukemia (AML) at UCBT, and median age at UCBT was 54 years. Twenty-four patients received a reduced-intensity conditioning (RIC) regimen, and 17 of 35 patients received total body irradiation (2 to 12 Gy)-fludarabine-cyclophosphamide (TCF) conditioning. The median follow-up was 24 months. The cumulative incidence of neutrophil recovery at 60 days was 80%. Fifteen patients relapsed after UCBT. The 2-year overall survival and event-free-survival (EFS) rates were 44% and 30%, respectively. All patients given TCF achieved neutrophil and platelet recovery, and the use of TCF was associated with superior EFS in the RIC population (44% versus 0%,

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$P = .001$). Patients with transformation to AML had similar outcomes to patients with less advanced stages. In conclusion, despite graft failure remaining a major concern, the role of UCBT in the management of MF, especially using RIC TCF-based regimens, deserves further investigation to improve results.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative option for patients with primary myelofibrosis (PMF) and myelofibrosis secondary to polycythemia vera or essential thrombocythemia (SMF). Several studies have shown survival rates of 40% to 60% after HSCT [1–5]. Transplant-related mortality (TRM) remains relatively high (10% to 40%) pursuant to inherent features of the underlying disease, such as its presentation commonly at an advanced age. HSCT is therefore usually reserved for the minority of younger higher risk patients [1–5].

The use of reduced-intensity conditioning (RIC) in patients with myelofibrosis (MF) has been explored, showing its applicability in older patients [6–9]. Umbilical cord blood transplantation (UCBT) is a valid alternative for patients lacking an HLA-matched donor [10,11] and double UCBT has extended this procedure to adults [12]. In a previous report, Takagi et al. [13] showed engraftment in 13 patients and a 4-year overall survival (OS) of 28% after RIC UCBT in 14 patients with hematological malignancies associated with bone marrow fibrosis, including 1 case of PMF and 1 of SMF. Another recent study compared outcomes of unrelated UCBT with other related and unrelated hematopoietic stem cell sources in patients with PMF given myeloablative (MAC) or nonmyeloablative conditioning. Lower neutrophil engraftment and higher TRM were reported after UCBT. The type of stem cell source did not appear to have an impact on OS (36% at 2 years), although the small number of UCBTs (N = 11) did not allow for definitive conclusions in this trial [14]. In this retrospective registry-based analysis, we describe UCBT outcomes in a series of patients with PMF or SMF.

METHODS

Data were retrieved from the Eurocord database and supplemented using the EBMT registry; a questionnaire was sent to the centers to complete missing data and to confirm the diagnosis. Neutrophil recovery was defined as an absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days and platelet recovery as a platelet count $\geq 20 \times 10^9$/L for 7 consecutive days without transfusion support. Graft failure (GF) was defined as never having reached neutrophils $\geq .5 \times 10^9$/L within the first 60 days after UCBT or documentation of autologous reconstitution by chimerism analysis. MAC was defined as a regimen containing either total body irradiation (TBI) with a dose $\geq$6 Gy, a dose of oral busulfan >8 mg/kg or, a dose of intravenous busulfan >6.4 mg/kg.

The Kaplan-Meier method was used to estimate OS and event free survival (EFS), considering GF, relapse, and death as events. Cumulative incidence was performed to estimate neutrophil and platelet recovery, relapse, and TRM. Considering the small number of patients, multivariate analysis was not performed. Statistical analysis was processed on SPSS version 19 (SPSS Inc., Chicago, IL) and S-Plus (MathSoft) software packages (Insightful Corp., Seattle, WA).

All patients provided informed consent for data treatment, according to the Declaration of Helsinki. This study was approved by the International Review Board of Eurocord and CMWP-EBMT.

Thirty-five patients with PMF (n = 20) or SMF (n = 15) who underwent a double (n = 22) or single (n = 13) UCBT between 2005 and 2012 in 23 EBMT centers were reported to Eurocord. Seven cases (3 PMF and 4 SMF) had transformed into acute myeloid leukemia (AML) at the time of UCBT: 4 were transplanted in complete remission. Patient, disease, and transplant characteristics are shown in Table 1.

The median age at UCBT was 54 years (range, 28 to 63). The median time from diagnosis of MF to UCBT was 27 months for PMF (range, 5 to 150) and 10 months for SMF (range, 1.4 to 111). The median time from AML diagnosis to UCBT was 6 months (range, .1 to 99). Fifteen patients (43%) underwent splenectomy before UCBT, and the median time from splenectomy to transplantation was 8 months (range, 2 to 206). Eleven patients (31%) received a MAC regimen and 24 (69%) a RIC. The most common conditioning regimen was TBI associated with cyclophosphamide and fludarabine (TCF, n = 17): of these, 4 patients received TCF with a myeloablative TBI dose of 12 Gy and 13 had a RIC with low-dose TBI 2 Gy. Cord blood units were 5/6 and 4/6 HLA matched to the recipient in 23% and 77% of the cases, respectively. Graft-versus-host disease (GVHD) prophylaxis was calcineurin inhibitor based for 34 patients (97%), given with mycophenolate mofetil in 19 of those patients (54%).

RESULTS

Hematological Recovery

Neutrophil recovery was achieved in 28 patients at a median time of 30 days (range, 11 to 60), whereas 19 had platelet recovery at a median time of 42 days (range, 13 to 91). Cumulative incidences of day 60 neutrophil recovery and day 100 platelet recovery were 80% (Figure 1A) and 54%, respectively. Among patients who achieved neutrophil recovery, 20 had evidence of full-donor or mixed chimerism (data missing for 1 patient). Overall, 14 patients experienced GF, and 4 of them received a subsequent HSCT (Table 1). Twelve-month survival was similar in patients with or without GF (48% versus 52%), whereas patients who did not achieve neutrophil recovery had poorer survival (14%). Indeed, some patients lived several years with autologous reconstitution and active disease (Table 1). According to the conditioning regimen, 8 of 11 MAC and 20 of 24 RIC achieved neutrophil recovery. Platelet recovery was achieved in 4 MAC and 15 RIC and was higher in patients who underwent splenectomy before UCBT (40% versus 70%, $P = .02$). Importantly, all patients receiving TCF as conditioning achieved both neutrophil and platelet recovery. Cell dose, disease characteristics, age, or cytomegalovirus serostatus had no significant impact on engraftment.

Graft-versus-Host Disease

Ten patients developed grades II to IV acute GVHD (7 grade II, 2 grade III, 1 grade IV) with a median time of onset of 33 days (range, 14 to 94). Among 18 patients at risk for chronic GVHD, 6 developed limited and 1 extensive chronic GVHD, with a median onset time of 167 days (range, 91 to 328).

Disease Status

Overall, 15 patients experienced progressive disease or relapse at a median of 7 months (range, 1 to 31) after UCBT: 3 were originally diagnosed with AML (in first complete remission at UCBT), 6 with PMF, and 6 with SMF (Table 1). Among patients with relapse, 7 had GF. One patient with AML relapsed 2.5 years after UCBT and received a second allogeneic HSCT from a matched unrelated donor, dying of veno-occlusive disease 92 days later. Among 11 patients alive at least 6 months after UCBT without relapse, 3 had available marrow biopsy results: 1 had complete resolution of marrow fibrosis (grade 0 at 21 months), 1 regressed from grade III to I