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Effect of Cord Blood Processing on Transplantation Outcomes after Single Myeloablative Umbilical Cord Blood Transplantation

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A B S T R A C T

Variations in cord blood manufacturing and administration are common, and the optimal practice is not known. We compared processing and banking practices at 16 public cord blood banks (CBB) in the United States and assessed transplantation outcomes on 530 single umbilical cord blood (UCB) myeloablative transplantations for hematologic malignancies facilitated by these banks. UCB banking practices were

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separated into 3 mutually exclusive groups based on whether processing was automated or manual, units were plasma and red blood cell reduced, or buffy coat production method or plasma reduced. Compared with the automated processing system for units, the day 28 neutrophil recovery was significantly lower after transplantation of units that were manually processed and plasma reduced (red cell replete) (odds ratio, .19; $P = .001$) or plasma and red cell reduced (odds ratio, .54; $P = .05$). Day 100 survival did not differ by CBB. However, day 100 survival was better with units that were thawed with the dextran-albumin wash method compared with the "no wash" or "dilution only" techniques (odds ratio, 1.82; $P = .04$). In conclusion, CBB processing has no significant effect on early (day 100) survival despite differences in kinetics of neutrophil recovery.

INTRODUCTION

Umbilical cord blood (UCB) transplantation has extended access to hematopoietic stem cell transplantation (HCT) to a diverse racial and ethnic population [1]. Recent data have suggested comparable results between UCB and grafts from matched adult unrelated donors in both the myeloablative and reduced-intensity transplantation setting [2-5]. However, unlike bone marrow or peripheral blood, UCB units are collected, cryopreserved, and, when needed, thawed and infused.

Although the Food and Drug Administration has issued guidance for manufacturing of cord blood for banking for unrelated transplantation, and the American Association of Blood Banks and the Foundation for Accreditation of Cellular Therapy have established standards for product manufacturing, practices at individual cord blood banks (CBB) vary tremendously. For example, UCB can either be collected in utero by trained obstetrical personnel and/or ex utero by trained staff of the UCB bank. The American Red Cross reported no difference in total nucleated cell (TNC) count, postprocessing $CD34^+$, or colony-forming units between the 2 methods, but transplantation outcomes were not assessed [6]. Similarly, processing of the UCB unit varies widely among and within the CBBs. In the earliest years of UCB banking, CBBs did not manipulate the product, other than diluting and adding dimethyl sulfoxide (DMSO), before freezing [7]. Today, most CBBs employ some form of volume reduction, which is generally achieved by depleting red blood cells, plasma, or both [8]. Each CBB has its own procedures, some of which may have evolved over the history of the bank. Most CBBs have adopted the plasma and red blood cell reduction method [9]. An alternative method is to deplete plasma but not red blood cells so that entrapment of nucleated cells, and possibly progenitor and stem cells, is avoided, with some degree of volume reduction associated with the removal of plasma [10,11].

Appropriate handling and thawing of UCB units at transplantation centers are equally important to successful transplantation outcomes. Pablo Rubinstein described a thawing procedure using a dextran and albumin solution to remove DMSO. The majority of transplantation centers adopted this approach, and nucleated cell count recoveries of 75% to 90% have been reported [12,13]. More recently, Barker et al. described a dilution-only "no wash" method with reconstitution in dextran-albumin for a final 5% DMSO concentration [14]. Nucleated cell count recovery was 86%, and there were no serious adverse infusion events. Finally, some centers have used a nonvolume-reduced (unmanipulated) thawing strategy and have demonstrated adequate engraftment [15]. The report of several life-threatening infusion reactions with UCB infusion have intensified the need to determine the optimal thawing practice [16].

The optimal processing techniques for UCB units are not established and whether transplantation outcomes differ by techniques is not clear. Therefore, we collected information on UCB processing at the CBBs and examined the data for an effect of processing methods at CBBs in patients who had undergone a single UCB transplantation for acute leukemia or myelodysplastic syndrome, the most common indications for allogeneic HCT. This report, the first of its kind, provides additional knowledge on whether practices at CBBs techniques influence hematopoietic recovery and early survival after UCB transplantation.

MATERIALS AND METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a working group of over 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT to a statistical center at the Medical College of Wisconsin or the data coordinating center at the National Marrow Donor Program. Banking practices at CBBs were obtained using a short survey, which addressed UCB unit processing at the banks. Data on UCB unit thawing at transplantation centers were obtained through standardized data collection forms developed by the CIBMTR. Patients provide written informed consent for participation in accordance with the Declaration of Helsinki. The institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program approved the study.

Patients

Included are 530 patients with acute myeloid leukemia (AML), acute lymphoid leukemia or myelodysplasia who received single unit unrelated UCB transplantation in the United States with a UCB unit from 1 of the 16 participating CBBs. All transplantations occurred in the United States between the years 2000 and 2011. Only recipients of myeloablative regimens, defined as having received total body irradiation dose of 1000 cGy or higher or busulfan dose greater than 9 mg/kg or melphalan dose greater than 150 mg/m^2, are included [17]. Recipients of multiple or expanded UCB units, reduced-intensity conditioning regimens, and transplantations for nonmalignant diseases were excluded.

CBB Practices

Sixteen publically funded CBBs in the United States participated in the survey. Using banking practices reported, 3 mutually exclusive groups were created (Table 1) based on the following: automated or manual processing at the CBB and whether units were plasma and red blood cell reduced, used the buffy coat production method, or were plasma reduced. All units contained DMSO and an hyperosmolar agent. Group 1 included units that were processed using an automated method that were plasma and red blood cell reduced ($n = 84$) or used the buffy coat production method ($n = 34$). Group 2 included manually processed units that were plasma and red blood cell reduced ($n = 274$) or used the buffy coat production method ($n = 5$). Group 3 included manually processed units that were plasma reduced. Of note, as the groups were created based on self-reported practices, some CBBs are represented in more than 1 group, as banking practices evolved over the study period. Further, group 3 represents a single CBB and the buffy coat production method is implemented at 3 CBBs and represented in group 1 ($n = 34$ from a single CBB) and group 2 ($n = 5$ from 2 CBBs).

Outcomes

The primary endpoint was hematopoietic recovery; *neutrophil recovery* was defined as achieving an absolute neutrophil count $\geq .5 \times 10^9$/L for 3