Cytotherapy, 2017; 19: 272–284

International Society for Cellular Therapy
ISCT®

CrossMark

HEMATOPOIETIC STEM CELL TRANSPLANTS

Lack of impact of umbilical cord blood unit processing techniques on clinical outcomes in adult double cord blood transplant recipients

SARAH NIKIFOROW[1,2], SHULI LI[3], KAREN SNOW[4], DEBORAH LINEY[1], GRACE SHIH-HUI KAO[5], RICHARD HASPEL[2,6], ELIZABETH J. SHPALL[7], BRETT GLOTZBECKER[1,2], R. ALEJANDRO SICA[8], PHILIPPE ARMAND[1,2], JOHN KORETH[1,2], VINCENT T. HO[1,2], EDWIN P. ALYEA III[1,2], JEROME RITZ[1,2], ROBERT J. SOIFFER[1,2], JOSEPH H. ANTIN[1,2], BIMAL DEY[2,4], STEVEN MCAFEE[2,4], YI-BIN CHEN[2,4], THOMAS SPITZER[2,4], DAVID AVIGAN[2,9], COREY S. CUTLER[1,2] & KAREN BALLEN[2,4]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [2]Harvard Medical School, Boston, MA, USA, [3]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Department of Medical Oncology, Massachusetts General Hospital, Boston, MA, USA, [5]Department of Medical Oncology, Tufts Medical Center, Boston, MA, USA, [6]Department of Pathology, Beth Israel Deaconess Hospital, Boston, MA, USA, [7]Department of Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, [8]Department of Medical Oncology, University of Illinois, Chicago, IL, USA, and [9]Medical Oncology, Beth Israel Deaconess Hospital, Boston, MA, USA

Abstract

Background aims. Despite widespread use of umbilical cord blood (UCB) transplantation and distinct practice preferences displayed by individual UCB banks and transplant centers, little information exists on how processing variations affect patient outcomes. *Methods.* We reviewed 133 adult double UCB transplants performed at a single center: 98 after reduced-intensity and 35 after myeloablative conditioning. Processing associated with contributing UCB banks and units was surveyed to identify differences in practice. We analyzed effect of selected variables on clinical outcomes of engraftment, dominance, transplant-related mortality, and survival. *Results.* Eighty-eight percent of banks queried currently practice red blood cell (RBC) depletion before cryopreservation. This reflects a shift in practice because previously 65% of banks employed RBC-replete processing methods (i.e., cryopreservation or plasma/volume reduction). Neither neutrophil nor platelet engraftment was affected by processing conditions analyzed. RBC depletion was not associated with clinical outcomes, except in 17 recipients of 2 RBC-replete units, where survival was better than that observed in 116 recipients of ≥1 RBC-depleted units (hazard ratio 3.26, $P = 0.004$). When analyzed by attributes of the dominant unit, RBC depletion, time in storage, bank years in existence, and inventory size did not affect clinical outcomes. Postthaw viability and CD34 dose were factors impacting engraftment. Notably, all RBC-replete units in this cohort were washed in dextran-human serum albumin before infusion. *Discussion.* These findings support continued utilization of the entire existing pool of cord blood units, despite recent trends in processing, and have important implications for banking resources and UCB selection practices.

Key Words: *processing, transplantation, umbilical cord blood*

Introduction

Several characteristics unique to individual umbilical cord blood (UCB) units correlate with clinical outcomes after UCB transplantation. Specifically, higher $CD34^+$ and total nucleated cell (TNC) dose and fewer human leukocyte antigen (HLA) disparities between unit and recipient are associated with higher rates of engraftment, lower transplant-related mortality (TRM) and improved overall survival (OS) [1–9]. Currently, some transplant centers may include aspects of processing before cryopreservation and attributes of UCB banks in their cord blood selection algorithms [10].

Correspondence: **Sarah Nikiforow**, MD, PhD, Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Dana 168, 450 Brookline Avenue, Boston, MA 02215. E-mail: sarah_nikiforow@dfci.harvard.edu

(Received 27 June 2016; accepted 27 October 2016)

ISSN 1465-3249
http://dx.doi.org/10.1016/j.jcyt.2016.10.016

There are more than 38 public cord blood banks in the United States and more than 100 banks in 25 countries [11]. Most of the published standards focus on labeling and basic quality measures [12–14]. Banking practices vary in terms of collection (*in utero* versus *ex utero*), time from collection to cryopreservation, processing method and storage conditions. Specific processing techniques include "cryopreservation" in which only a cryopreservation agent is added before freezing and "plasma/volume reduction" in which cells are concentrated by centrifugation, reducing volume and storage requirements. Units undergoing such processing are termed "RBC-replete." Other units are "RBC depleted" using sedimentation agents, such as hydroxylethyl starch (hetastarch), by processing in automated systems. Although RBC depletion may result in cell loss during processing, it dramatically reduces volume, allowing banks to store more UCB units in a finite space [15]. Some of these strategies, such as the Sepax, are considered "RBC-reduction methods" because there can be minimal RBC content in the processed UCB unit [16]. However to simplify the following analysis, all such methods are termed "RBC depleted." Clinically, RBC depletion allows for bedside thaw and dilution without the concern for dangerous hemolytic infusion reactions, regardless of ABO status. Supplying banks also differ as to number of units in inventory and years in existence, both surrogate measures of bank experience.

Banking practice patterns continually evolve to optimize manufacturing, but data to guide changes in the field are limited. Initial studies of cord blood processing techniques, such as RBC depletion, use of automated processing systems, and washing following thaw, focused on cellular endpoints such as total nucleated cell (TNC) and CD34 count recovery rather than important clinical outcomes such as engraftment and survival [17–20]. UCB selection algorithms have concurrently evolved, and certain transplant centers may prioritize UCB units from a subset of banks or units processed in a particular manner. For example, in one prior study, bank accreditation and smaller unit volume (often linked with RBC-depletion) was associated with post-thaw $CD34^+$ cell viability. This cohort also demonstrated that viable $CD34^+$ dose of the dominant unit impacted time to engraftment [21].

In this retrospective analysis, we first assessed current and prior banking/processing practices to identify aspects of variability among individual UCB banks and units. Specific variables among bank practices and unit attributes were then correlated with patient-level clinical outcomes following double UCB unit transplantation. The double UCB model was chosen to reflect the current practice in many adult transplant centers within the United States. The goal of this study was to assess whether UCB bank attributes and processing conditions affect engraftment, transplant-related mortality and survival after adult double UCB transplantation (dUCBT), employing standard thawing and washing practices. Our findings have implications for utilization of many UCB units within the more than 700 000 units banked worldwide.

Methods

Study eligibility and design

Consecutive adults (≥18 years old) undergoing dUCBTs between January 2003 and June 2011 at Dana-Farber/Harvard Cancer Center (DF/HCC) were included, involving three hospitals with standardized treatment protocols, UCB unit thawing and washing procedures and supportive care approaches (Dana-Farber Cancer Institute, Massachusetts General Hospital, and Beth Israel Deaconess Medical Center). The primary objective was to determine whether processing and bank practices influenced days to neutrophil engraftment. Secondary outcomes included platelet engraftment, unit dominance, 100-day and 1-year TRM and OS. The Human Subjects Committees of DF/HCC Institutional Review Board approved this research.

Recipients of single UCBT, of prior allogeneic stem cell transplantation, with aplastic anemia or of any unit that had undergone *ex vivo* manipulation were excluded. HLA typing for HLA-A, -B and -DR was performed at the allelic level. Unit characteristics and processing methods used at cryopreservation were gathered from primary documents provided by distribution sites. All 48 banks contributing units and still in operation were contacted between October 2012 and June 2013 to clarify current and prior practices and changes over time; 34 responded. Specific practices queried were processing before cryopreservation (i.e., minimal manipulation, plasma/volume reduction, or RBC-depletion), use of sedimentation agents, use of automated processing devices, use of anticoagulants and additives, the method of collection (i.e., *in utero* or *ex utero*), required time from collection to cryopreservation, use of controlled-rate freezing, mode of storage in liquid nitrogen, size of inventory and years the bank had been in existence. Bank accreditation status as of September 2016 was determined from Foundation for the Accreditation of Cellular Therapy (FACT) and AABB websites.

Infusion site practices

In all three DF/HCC cell-processing facilities, RBC-replete units were thawed, washed in dextran 40/ 5% human serum albumin mix, then reconstituted in 1:1 dextran/albumin (final concentration 5% each) [22,23]. One facility omitted washing for RBC-depleted units (n = 23) and reconstituted in a 1:1 dextran/albumin