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Impact of Long-Term Cryopreservation on Single Umbilical Cord Blood Transplantation Outcomes



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ABSTRACT

Umbilical cord blood (UCB) may be collected and cryopreserved for years before use. In vitro and murine models suggest that the duration of storage does not affect UCB progenitor cell performance; however, the impact of UCB age on clinical outcomes has not been definitely defined. This study sought to determine the effect of UCB unit cryopreservation time on hematopoietic potency. We analyzed 288 single UCB units used for transplantation from 1992 to 2013, with unit cryopreservation time ranging from .08 to 11.07 years. UCB unit post-thaw characteristics were examined, including percent recovery of total nucleated cells (TNC). The number of years the UCB unit spent in cryopreservation had no impact on TNC recovery nor UCB unit post-thaw viability. Duration of cryopreservation also had no impact on neutrophil or platelet engraftment in single UCB transplantations. These results show that UCB units can undergo cryopreservation for at least 10 years with no impact on clinical outcomes.

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INTRODUCTION

The first successful umbilical cord blood (UCB) transplantation was performed in 1988 [1], and since that time, the ability to cryopreserve and bank UCB units has remained an essential component of their use in hematopoietic stem cell transplantation. The use of UCB as a donor source has continued to grow, and there are currently over one half a million UCB units cryopreserved in the worldwide cord blood inventory [2].

Although cryopreservation is universally practiced in cord blood banking, the impact on progenitor cell function has been only partially addressed. Broxmeyer et al. demonstrated that UCB units stored for up to 20 years do not lose function when used in vitro and in murine assays of progenitor cell function [3,4], and the St. Louis group reported no significant influence on clinical outcome after short-term cryopreservation [5]. Parmar et al. recently reported on

clinical outcomes for cryopreserved units, but they only documented 15 UCB units older than 5 years [6]. Hence, there is still no conclusive answer to the question of whether long-term cryopreservation affects UCB transplantation outcomes. Storage of UCB units comes at a financial cost to cord blood banks [7,8], which is ultimately passed on to the patient, transplantation institution, and the health care system as a whole [9–11]. If long-term cryopreservation is detrimental to UCB transplantation outcomes, the current model of cord blood banking must be called into question. Alternatively, if the duration of cryopreservation has no impact on clinical outcomes, this provides evidence for cord blood banks to continue the current model of cryopreservation, long-term storage, and distribution of UCB units, to provide a rapidly accessible donor source for transplant recipients worldwide.

In this study, we set out to determine whether duration of cryopreservation influenced single UCB transplantation outcomes. We also examined the effect of cryopreservation on post-thaw UCB unit characteristics.

METHODS

Study Design

This was a retrospective review of 416 patients who underwent single UCB transplantation at the University of Minnesota between 1992 and 2013. Reasons for exclusion from the analysis included no available date of

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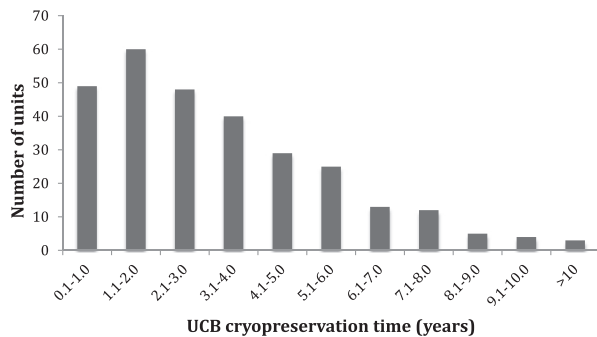


Figure 1. Umbilical cord blood units by duration of cryopreservation. A total of 62 umbilical cord blood units were cryopreserved for more than 5 years.

collection for the UCB unit ($n = 125$) and patients who did not receive conditioning before receiving the UCB unit ($n = 3$). Patients were treated on protocols approved by the University of Minnesota institutional review board, and written consent was obtained from all patients, their parents, or guardians in accordance with the Declaration of Helsinki.

UCB Unit Processing

On delivery of UCB units to the University of Minnesota Molecular and Cellular Therapeutics facility, units were inspected and then transferred and maintained in vapor phase of liquid nitrogen storage until the day of infusion. All UCB units were thawed and washed per the method of Rubinstein et al. [12]. Before the wash, ABO/Rh typing of the unit was performed. After the

wash and before release for infusion, samples were taken for assessment of viability, total nucleated cell dose (TNC), CD34⁺ dose, and colony-forming units-granulocyte macrophage (CFU-GM). Viability was assessed using the acridine orange and propidium iodide method [13] and 7-aminoactinomycin D (by flow cytometry). Flow cytometry was performed as per the International Society of Hematotherapy and Graft Engineering specifications using a dual platform, with ammonium chloride lysis for red cells followed by washing and staining.

Definitions and Outcome Analysis

UCB units were analyzed based on the duration of cryopreservation of the UCB unit. The TNC recovery was defined as the total TNC recovered at thaw, expressed as a percentage of the total TNC count reported before freezing.

Neutrophil and platelet engraftment were defined as previously described [14–16]. Cox regression analysis was used to perform univariate and multivariate analysis of patient and UCB unit factors and their influence on outcomes. The following variables were assessed for their association with neutrophil and platelet engraftment: duration of cryopreservation, post-thaw TNC/kg, post-thaw CD34⁺/kg, viability post-thaw, post-thaw CFU/kg, UCB unit-recipient ABO match, UCB unit-recipient HLA match, year of transplantation, type of conditioning regimen used, recipient gender, recipient age, and recipient cytomegalovirus status. After 2005, patients undergoing UCB transplantation at the University of Minnesota have not routinely received antithymocyte globulin as part of their myeloablative conditioning regimen. As such, year of transplantation was examined as patients who underwent hematopoietic stem cell transplantation before 2006 compared with the more recent era.

RESULTS

Cell Recovery

There were 288 single UCB transplantations eligible for analysis, with the duration of cryopreservation of the UCB units ranging from .08 to 11.07 years (Figure 1). The median post-thaw values for TNC were 11.3×10^8 cells (range, .97 to 38.41) and 12.9×10^6 cells (range, .18 to 131.5) for CD34⁺ cells. The median post-thaw nucleated cell viability for the cohort was 72% (range, 30% to 94%) and median post-thaw total CFU-GM was 1.1×10^6 (range, 0 to 58.81). The median TNC recovery was 76% (range, 30% to 108%). Duration of cryopreservation of the UCB unit had no significant impact on the median post-thaw TNC ($P = .22$), CD34⁺ ($P = .28$), or CFU-GM ($P = .68$). Duration of cryopreservation of the UCB unit also had no impact on post-thaw nucleated cell viability and TNC recovery (Figure 2A,B).

Neutrophil Engraftment

Neutrophil engraftment for the cohort was 94% (95% confidence interval, 91% to 96%), with a median time to neutrophil recovery of 20 days (range, 0 to 41). When duration of cryopreservation of the UCB unit was analyzed as a continuous variable in multivariate analysis, there was no impact on neutrophil engraftment ($P = .15$, data not shown). UCB units were also analyzed in tertiles based on time spent in cryopreservation (0 to 2 years, 2.1 to 4 years, >4 years) and tested in univariate (Table 1) and multivariate analysis (Table 2). There was no association of duration of cryopreservation on the probability of neutrophil engraftment. Other covariates, including CD34⁺ dose, CFU-GM, and year of transplantation were independently significant factors identified in multivariate analysis (Table 2). Duration of cryopreservation of the UCB unit also had no significant impact on time to neutrophil engraftment (Figure 3A).

Platelet Engraftment

Platelet engraftment at 1 year was 74% for the cohort (95% confidence interval, 67% to 81%), with a median time to platelet recovery of 48 days (range, 10 to 224). When analyzed as a continuous variable in multivariate analysis,

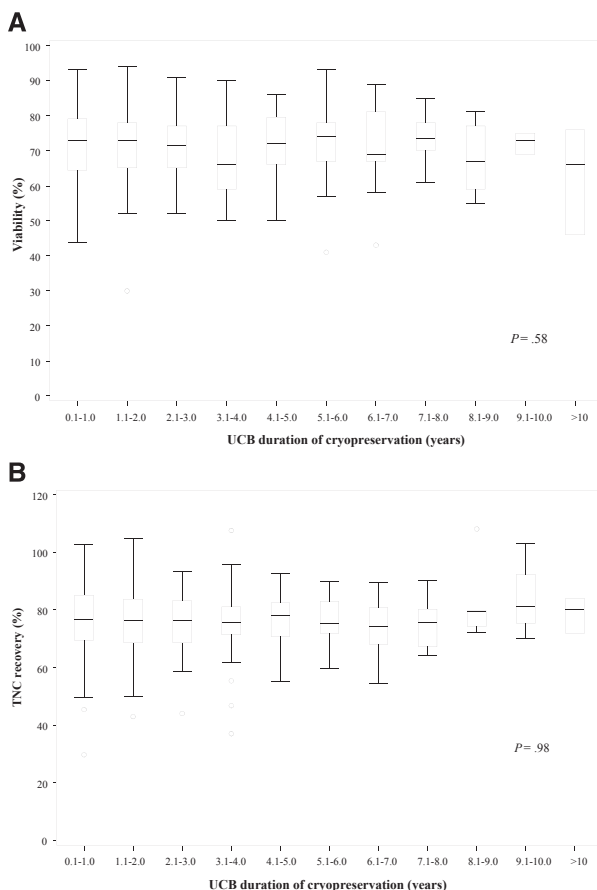


Figure 2. Post-thaw nucleated cell viability (A) and total nucleated cell recovery (B) based on umbilical cord blood unit duration of cryopreservation. There was no statistically significant difference in post-thaw nucleated cell viability ($P = .58$) or total nucleated cell recovery ($P = .98$) based on duration of cryopreservation.

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