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Low rate of infusional toxicity after expanded cord blood transplantation

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Abstract

Background aims. Umbilical cord blood (CB) is used with increasing frequency to restore hematopoiesis in patients with bone marrow transplant who lack a suitable human leukocyte antigen–matched donor. CB transplantation is limited by low cell doses and delays in neutrophil and platelet engraftment. CB progenitors expanded *ex vivo* before transplantation provide more rapid hematopoietic and immune reconstitution as well as less engraftment failure compared with unmanipulated CB. However, the safety of infusing double and *ex vivo*–expanded CB has not been systematically examined. *Methods.* We reviewed the immediate adverse events (AE) associated with the infusion of CB occurring within 24 hours in 137 patients enrolled in clinical CB transplant trials at the MD Anderson Cancer Center from February 2004 to May 2010. All patients received an unmanipulated CB unit followed by infusion of a second unmanipulated CB unit or a second CB unit expanded *ex vivo* with the use of cytokines in a liquid culture system or in mesenchymal stromal cell co-cultures. *Results.* A total of three grade 2 and two grade 3 infusion reactions occurred within 24 hours of CB transplantation. This resulted in an AE rate of 3.7%. The majority of AEs manifested as signs of hypertension. No association with patient age, sex, disease status, premedication, ABO compatibility or total infusion volume was observed. In summary, the incidence of infusion-related toxicities in patients who receive unmanipulated and *ex vivo*–expanded double CB transplantation is low. *Conclusions.* We conclude that the infusion of unmanipulated followed by expanded CB products is a safe procedure associated with a low probability of inducing severe reactions.

Key Words: *cell culture, cord blood transplantation,* ex vivo *expansion*

Introduction

Umbilical cord blood (CB) is used with increasing frequency to restore hematopoiesis in patients with bone marrow transplant who lack a suitable human leukocyte antigen (HLA)-matched donor because of its ease of procurement as well as a decreased incidence of graft-versus-host disease (GVHD) in comparison with bone marrow transplantation. CB transplantation, however, is limited by low cell doses, which results in delayed neutrophil and platelet engraftment as well as high rates of engraftment failure (1–5). The use of two CB grafts has become a standard practice for adult patients, providing a higher cell dose and less engraftment failure compared with single CB transplant recipients (6–8). An alternative method to increase the total neutrophil count is to expand CB progenitor cells *ex vivo*. The *ex vivo* expansion of CB before transplantation allows for the administration of higher cell doses and has been demonstrated to provide more rapid neutrophil and platelet engraftment as well as less engraftment failure compared with unmanipulated CB (9–11).

A variety of methods are currently under investigation for expanding CB *ex vivo*, which include static liquid cultures alone (9,12) or in conjunction

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with notch-ligand (10), as well as stromal co-culture (11) and continuous perfusion culture systems (13). CB culture in the presence of various proteins, such as Notch ligand or with mesenchymal stromal cell (MSC) co-cultures, greatly increases the number of CD34+ progenitor cells with repopulating ability and subsequently leads to more rapid myeloid engraftment (10).

Although the adverse events (AE) associated with traditional stem cell transplants are well defined, the relative safety regarding the infusion of double and *ex vivo*–expanded CB transplantation has not been widely reported. We review immediate AEs occurring within 24 hours of infusion among 137 patients receiving double CB transplantation with either two unmanipulated or one unmanipulated plus one expanded CB unit at MD Anderson Cancer Center (MDACC) between February 2004 to May 2010.

Methods

Patients

All patients were treated on MDACC institutional review board–approved protocols conducted under Investigational New Drug (IND) after approval by the US Food and Drug Administration. This retrospective chart review was also approved by the institutional review boards at Baylor College of Medicine and MDACC.

All patients received either a myeloabative or non-myeloablative preparative regimen on days −8 through −2, followed by infusion of two CB units on day 0. All patients were infused with a single unmanipulated CB unit followed by the immediate infusion of a second unit that was unmanipulated (n = 48) or expanded *ex vivo* in either a liquid culture system (n = 46) (14) or in MSC co-cultures (n = 43) (11). Patients were pre-medicated with 25 mg intravenous diphenhydramine and 100 mg intravenous hydrocortisone before each CB unit infusion. Patients intolerant of diphenhydramine were pre-medicated with hydrocortisone alone (Table I).

CB processing and infusion

Unmanipulated CB units were thawed, washed with Dextran-40 Hospira, Lake Forest, IL, USA and human serum albumin Baxter, Deerfield, IL, USA and infused. For cells expanded in liquid culture, $CD133^+$ cells were selected with the use of the Miltenyi Clinimacs columns Miltenyi Biotec, Auburn, CA, USA and cultured for 14 days in Minimum Essential Medium (MEM)-α medium (Hyclone, Logan, UT, USA) containing granulocyte colony-stimulating factor (G-CSF; Amgen, Thousand Oaks, CA, USA), stem cell growth factor (SCF; Cellgenix, Freiburg, Germany), thrombopoietin (TPO; R&D Minneapolis, MN, USA) and Flt-3 ligand (Flt3-L; Cellgenix) (14). For cells grown with MSCs, MSC co-cultures were generated by culturing enriched CB mononuclear cells for 14 days on MSC monolayers in serum-free medium (CellGenix) containing G-CSF, SCF, Flt-3L and thrombopoietin (11). On day 7, the non-adherent cells were transferred to a bag with additional media and growth factors while the flasks with the adherent cells were similarly re-fed. On culture day 14, all the cells from the bags and flasks were combined, washed and infused. MSCs were obtained from the bone marrow of haploidentical family or third-party unrelated donors.

Grading of AEs

Immediate AEs were monitored after each CB unit infusion every 15 minutes for the first hour, hourly for 2 hours and then at 24 hours after the second CB infusion. AEs were graded on a scale of 1–5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

Statistical methods

The analyses were primarily descriptive, including the median and range of clinical variables. Comparisons between multiple groups were performed with the use of analysis of variance and Student's t test for continuous variables, and χ^2 test and Fisher's exact tests were performed for categorical data. A value of $P < 0.05$ was considered statistically significant.

Results

The median age of all enrolled patients was 42.8 years (range, 3–74) and was similar for recipients of unmanipulated versus expanded CB units. There was a significant sex difference among the unmanipulated and MSC expanded cohorts (Fisher's exact test; $P = 0.01$). Most patients received CB transplantation for the treatment of acute leukemia (acute myelogenous leukemia: n = 56, acute lymphocytic leukemia: n = 26). A smaller subset of patients was treated for chronic leukemia (chronic myelogenous leukemia: n = 6, chronic lymphocytic leukemia: n = 14) and lymphoma (Hodgkin: n = 9, non-Hodgkin: n = 21). All four patients with myelodysplastic syndrome received cytokine-expanded CB. Both the cytokine expanded and MSC-expanded cohorts were noted to have a larger number of patients having undergone prior stem

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