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Improved Prediction of CD34$^+$ Cell Yield before Peripheral Blood Hematopoietic Progenitor Cell Collection Using a Modified Target Value–Tailored Approach

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Article history:
Received 31 July 2015
Accepted 23 November 2015

Key Words:
Peripheral blood collection
Apheresis
Hematopoietic progenitor cells

A B S T R A C T

The most commonly used stem cell source for both autologous and allogeneic transplantation is mobilized peripheral blood hematopoietic progenitor cells collected by apheresis. In the 1990s, an Italian group used the correlation between the preapheresis peripheral blood CD34$^+$ cell count and the final number of CD34$^+$ cells collected to devise a formula for "target value–tailored" (TVT) apheresis. Using local patient data, the Canadian Blood Services Stem Cell Laboratory created a similar model to determine the blood volume to process during apheresis collection. The objectives of this study were to determine the correlation between the number of CD34$^+$ cells predicted by the TVT formula and the actual number of CD34$^+$ cells collected and to determine whether the TVT formula remains predictive when applied to an external data set. All apheresis collections performed at the Ottawa Hospital between January 1, 2003 and October 2, 2013 were reviewed. The primary outcome was the correlation between the number of CD34$^+$ cells predicted by the TVT formula and the actual number of CD34$^+$ cells collected on day 1 of apheresis. For the external data set, all autologous collections performed at the London Health Sciences Centre between December 1, 2008 and December 1, 2013 were reviewed. The external data set was divided into test and validation sets to determine whether a model could be created to predict the final number of CD34$^+$ cells collected on day 1 based on the preapheresis CD34$^+$ count. A total of 1252 collections were included in the analysis. The Ottawa data set included 1012 collections, 836 of which were autologous and 176 of which were from donors. Of the autologous collections in Ottawa, 764 (92.5%) were first collections. In 759 (91%) collections, chemotherapy plus granulocyte colony–stimulating factor (G-CSF) was used as the mobilization regimen. In 747 collections (89%), only 1 collection day was required to achieve the desired number of CD34$^+$ cells. The TVT estimate was highly predictive of the number of CD34$^+$ cells $\times$ 10^6/kg actually collected on apheresis day 1 ($r = .90$, $P < .0001$). The London data set included 240 autologous collections. All mobilizations were with G-CSF alone. For the test set, the precollection CD34$^+$ count was highly predictive of the number of CD34$^+$ cells $\times$ 10^6/kg collected on day 1 of apheresis. Applying this model to the validation set, the correlation between the predicted and final and day 1 CD34$^+$ cells $\times$ 10^6/kg count was .9186 ($P < .0001$). Using a modified TVT approach, the preapheresis CD34$^+$ count can be used to accurately predict the number of CD34$^+$ cells $\times$ 10^6/kg collected on day 1. This approach can be applied at other centers and for different diseases and mobilization regimens. This method can be used to individualize the blood volume processed and, thus, optimize resource utilization.

INTRODUCTION

High-dose chemotherapy followed by autologous hematopoietic progenitor cell transplantation improves response rates and overall survival in patients with multiple myeloma [1,2] and relapsed lymphoma [3,4]. The success of

Financial disclosure: See Acknowledgments on page 767.

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http://dx.doi.org/10.1016/j.bbmt.2015.11.016
1083-8791/

this treatment depends on collecting a minimum of 2×10^6 $CD34^+$ cells/kg. The majority of transplantation centers use peripheral blood as the hematopoietic progenitor cell (HPC) source before autologous transplantation [5]. After mobilization, typically using granulocyte colony–stimulating factor (G-CSF) with or without chemotherapy, HPCs are collected by apheresis. Response to the mobilization regimen often depends on patient- and procedure-related variables. Individual patient variables include age [6], type and extent of prior therapies [7-9], and the extent of disease involvement of the bone marrow [10]. Procedural variables include the mobilization regimen used [11], the precollection $CD34^+$ cell count [12], and specifics of the apheresis technique [13]. Most of these variables cannot be modified, whereas others, such apheresis technique and strategy, can be optimized to ensure timely and successful mobilization.

The goal of apheresis collection is to collect enough $CD34^+$ cells to ensure timely neutrophil and platelet recovery. Historically, the target has been 5×10^6 $CD34^+$ cells/kg [14-17] and there is no apparent benefit to collecting more. Continuing apheresis after an appropriate number of $CD34^+$ cells has been obtained requires more of the patient's time, may place the patient at increased risk (of citrate reactions or thrombocytopenia, for example), and is an inefficient use of health care resources, including personnel time and physical space. The method used to predict the final product $CD34^+$ cell yield, and thus the whole blood volume to process during apheresis collection, has not been standardized. Approaches used in Canadian centers vary and include processing a standard volume of 20 L to 25 L on all patients, crude estimations based on the precollection peripheral blood $CD34^+$ cell count, mathematical formulae incorporating the precollection peripheral blood $CD34^+$ cell count and the patient's weight, and real-time measurement of the product $CD34^+$ cell count during apheresis (personal communication with transplant program directors).

In the mid-1990s, an Italian group used the correlation they observed between the preapheresis peripheral blood $CD34^+$ cell count and the number of $CD34^+$ cells collected to devise a formula for "target value–tailored" (TVT) apheresis. They demonstrated that they could apply this formula to accurately determine the blood volume to process during apheresis collection to harvest the desired number of $CD34^+$ cells [18]. Using local patient data, the Canadian Blood Services Stem Cell Laboratory (CBS SCL) in Ottawa has created a similar regression model for predicting the final product $CD34^+$ cells based on the precollection peripheral blood $CD34^+$ cell count. This formula has been applied to all peripheral blood HPC collections at The Ottawa Hospital, from both autologous and allogeneic donors, for over a decade.

We reviewed all peripheral blood HPC apheresis collections performed at our institution over a 10-year period. The objective was to determine the correlation between the number of $CD34^+$ cells predicted by the TVT formula and the actual number of $CD34^+$ cells collected. We also reviewed all peripheral blood HPC collections performed at a second Canadian center over a 5-year period to determine whether the TVT formula remained predictive when applied to an external data set.

METHODS

All HPC apheresis collections performed at the Ottawa Hospital between January 1, 2003 and October 2, 2013 were reviewed. Collections were identified from the Ottawa CBS SCL database, a database that prospectively records preapheresis information, including demographic information, transplantation indication, preapheresis peripheral blood white blood cell, $CD34^+$ cell count, and final collection product information, including blood volume processed and $CD34^+$ cells/kg.

The primary outcome was the correlation between the number of $CD34^+$ cells predicted by the TVT formula and the actual number of $CD34^+$ cells collected on day 1 of apheresis. Secondary outcomes included the correlation between the number of $CD34^+$ cells predicted by the TVT formula and the final number of $CD34^+$ cells collected, the proportion of patients collecting at least 2×10^6 $CD34^+$ cells/kg and at least 5×10^6 $CD34^+$ cells/kg, and the proportion of patients proceeding to transplantation.

Peripheral Blood HPC Collection

Preapheresis $CD34^+$ cell counts were measured using the Beckman Coulter Epicx XL flow cytometer from January 1, 2003 to January 31, 2011 and the Beckman Coulter FC500 flow cytometer from February 1, 2011 to October 2, 2013. Large volume apheresis collections were performed using the COBE Spectra cell separator (version 6.0; COBE Laboratories, Lakewood, CO). Intravenous access was peripheral in all patients in whom it could be achieved. A minority of patients required central lines. Using a dual needle system, whole blood was processed at 30 mL/minute to 70 mL/minute up to a maximum of 25 L per day. The anticoagulant used was Acid Citrate Dextrose Solution A (Baxter, Lake Zurich, IL).

TVT Model

Institutional $CD34^+$ cell/kg estimation curves were initially constructed in 1999. The precollection peripheral blood $CD34^+$ cells/uL was plotted against the $CD34^+$ cells/kg per 10 L whole blood volume processed by apheresis. The regression model created formed the basis for subsequent prediction of $CD34^+$ cells/kg per 10 L processed from the precollection $CD34^+$ cells/uL for individual patients and healthy donors.

Validation Study

For the external data set, all autologous collections performed at the London Health Sciences Centre between December 1, 2008 and December 1, 2013 were reviewed. At this center, apheresis collections were done using the Spectra Optia Apheresis System (Terumo BCT, Lakewood, CO). Central venous access was obtained and whole blood was processed at 40 mL/minute to 80 mL/minute for a total of 3 times the total blood volume. Acid Citrate Dextrose Solution A was used for anticoagulation.

The external data set was divided into test and validation sets to determine whether a model could be created to predict the final number of $CD34^+$ cells collected on day 1 based on the preapheresis $CD34^+$ count.

Statistical Analysis

Baseline characteristics were analyzed using measures of central tendency and dispersion, where appropriate. Regression analysis was used to construct and refine the TVT curves. Spearman's rank correlation was used to determine the correlation between the predicted and actual $CD34^+$ cells/kg.

RESULTS

A total of 1252 collections were included in the analysis. The Ottawa data set included 1012 collections; 836 were autologous and 176 were from allogeneic donors. The patient characteristics are shown in Table 1. The most common indications for collection were multiple myeloma and aggressive non-Hodgkin lymphoma. Of the autologous mobilizations in Ottawa, 764 (92.5%) were first collections, 60 (7.3%) were second collections, and 2 were third collections. In 757 (91%) collections, chemotherapy plus G-CSF was used as the mobilization regimen. Cyclophosphamide plus G-CSF was used in 522 (66%) collections, cytosine arabinoside-cisplatin-dexamethasone was used in 124 (16%), ifosfamide-carboplatin-etoposide was used in 61 (8%), and various chemotherapy regimens plus G-CSF were used in 50 (6%). Plerixafor plus G-CSF was used in 34 (4%) of collections.

In 747 collections (89%), only 1 collection day was required to achieve the desired number of $CD34^+$ cells. The median precollection $CD34^+$ cell count was 3.26 (range, 0 to 1130)/μL. The median volume processed was 20 L. In 257 collections (25%), fewer than 15 L were processed and in 106 (10%), fewer than 10 L were processed. The TVT estimate was