A Method to Predict the Yield of Peripheral Blood Stem Cells Collected by Large Volume Leukapheresis

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Abstract

Background: Collection of peripheral blood stem cells (PBSC) by leukapheresis has become the dominant method in allogeneic hematopoietic stem cell donation and also overpassed bone marrow donation in autologous transplantations. The circulating CD34 positive cells immediately prior to PBSC collection strongly correlate with the PBSC yield and have used to monitor donor’s response to bone marrow mobilization.

Methods: In this prospective study, a prediction method for PBSC collection that has been used in our facility was provided. Prediction accuracy is evaluated by comparison of predicted CD34 values to real PBSC yield.

Results: The prediction method was used to determine first if a standard procedure with 12 L of blood processing could achieve the collection goal. Thirty seven donors were considered to have adequate PBSCs. Thirty four of them had a CD34 count above the target and only one donor had a CD34 count significantly below the target. For the donors whose PBSC were considered inadequate, an extended collection was performed based on the predicted blood volume that needed to be processed. The number of overestimated predictions was essentially the same as the number of underestimated predictions.

Conclusion: The proposed prediction method was successful in identifying donors who needed extended collection without causing unnecessary prolongation of the leukapheresis procedure.

Keywords: Leukapheresis; Stem cell; PBSC; CD34 cells

Introduction

Collection of peripheral blood stem cells (PBSCs) by leukapheresis has become the preferred approach in allogeneic hematopoietic stem (HSC) donations as well as autologous donations [1-3] because of fewer side-effects [4] and quick resolution of donation-related symptoms in donors [5], and shorter time to engraftment and faster immune reconstitution in recipients [6]. The collection procedure follows a bone marrow mobilization process and granulocyte colony-stimulating factor has been the most commonly used reagent [6,7]. CD34 is a cell surface molecule expressed on hematopoietic stem cells (HSC) and considered the best cell marker for monitoring PBSC mobilization. Because previous studies have shown that the amount of circulating CD34+ cells prior to collection strongly correlates with the PBSC yield [8], pre-CD34 count has been used to determine the time for performing leukapheresis in autologous donors [9]. In contrast, pre-CD34 count in healthy allogeneic donors is usually not monitored before PBSC collection. Instead, leukapheresis is performed on the fifty day, after the donor is administered the last dose of G-CSF. In the situation of volunteer allogeneic donations, the PBSC recipients are almost always in remote sites and even the donors may come from different cities. Thus, it would be convenient for both the donors and the transplantation coordinating facilities to know when the collection can be completed so they can arrange transportation, etc. Moreover, although PBSC collection is generally a safe, well tolerated procedure [10], procedure related adverse events still occurs [11] and the length of PBSC collection has been associated with more adverse events and bad donation experience [12,13]. Therefore, it is desirable to have a reliable prediction method in order to avoid unnecessarily prolonged collection for the safety of donors. Some prediction methods have been proposed and have proven useful [14,15]. In the present study, we introduced a simple method to predict PBSC yield based on pre-CD34 count. This method has been used in more than a thousand PBSC collections and proven efficient and accurate.

Material and Methods

Donors

A total of 69 healthy volunteer allogeneic donors who underwent PBSC donation between November, 2009, and December, 2011 were enrolled in this study. All of these volunteers agreed to the PBSC mobilization and collection procedures and gave thoroughly informed consent. This study was approved by the Institutional Review Board at Houston Methodist Hospital. The donor characteristics are summarized.

Mobilization and collection of PBSC

All donors were given human recombinant G-CSF (filgrastim) 10 μg/kg/day subcutaneously for 5 days to mobilize PBSC. On the fifth day, PBSC harvest was performed on the COBE spectra (Caridian BCT, Lakewood, CO). A minimum of 12 L of whole blood was processed with anticoagulant citrate dextrose solution (ACD-A) in about 4 h. The
decisions whether and how much to extend the procedure were made by the medical director and the donor based on the pre-collection CD34 count. No procedure exceeded a total of 24 L of whole blood processing, regardless of what the CD34 count was.

**Body weight and blood volume determination**

The donor’s actual body weight was obtained on the day of PBSC collection. Total blood volume (TBV) was determined by Nadler’s formula (blood volume in liters, height in meters, and weight in kilograms) [16]:

\[
TBV \text{ (males)} = (0.3669) \times (\text{height})^3 + (0.03219) \times (\text{weight}) + 0.6041
\]

\[
TBV \text{ (females)} = (0.3561) \times (\text{height})^3 + (0.03308) \times (\text{weight}) + 0.1833
\]

**Clinical laboratory test**

A baseline complete blood count (CBC) with differential was obtained as part of the donor workup, performed about three weeks before PBSC collection. Blood samples drawn immediately before apheresis were sent to the clinical hematology laboratory for immediate CBC with differential and to the flow cytometry laboratory for CD34+ cell count. Post-apheresis blood samples and collected PBSC products were tested in the same manner.

**Statistical analyses**

Data were analyzed with the SPSS 24.0 software package (IBM, Chicago, IL). Where not indicated otherwise, variables were recorded as mean values and standard deviation, and a t test and one-way analysis of variance were applied. A value of \( p < 0.05 \) was considered statistically significant.

**Results**

**Correlation between pre-CD34 count and CD34 positive cell collected**

The CD34+ cell count, as measured immediately before leukapheresis (pre-CD34), has a strong correlation with the amount of CD34 positive cells collected at the end of leukapheresis [17,18]. In order to determine the correlation strength between pre-CD34 and CD34 yield after leukapheresis in our donor population, we studied 42 healthy volunteer donors, all of whom underwent a collection with 12 liters of blood processed (Figure 1).

The pre-CD34 strongly correlated with CD34 cells collected after 12 L of blood processing (\( p = 0.001 \)), with a correlation coefficient (\( r \)) of 0.865, which is similar to previous reports. In contrast, correlation between the count of WBC count, platelet, or neutrophil and CD34 yield was weaker than the correlation between pre-CD34 and CD34 yield (Data not shown). These results were consistent with previous findings and supported the use of pre-CD34 count to predict final CD34 yield.

**Prediction formula of CD34 yield in PBSC collection based on donor’s pre-CD34 count**

We have developed a formula to estimate the CD34 yield based on donor’s pre-CD34, which has been used in both autologous donors and healthy volunteer donors, as follows,

\[
\text{Predicted CD34 per kg of receipt BW (× 10^6/kg)} = \text{pre-CD34} \times k \times \left(\frac{\text{Donor BW/receipt BW}}{12}\right)
\]

Where \( k \) is a coefficient, related to the efficiency of the collection (\( k = 0.085 \) in our facility), BW represents body weight (kg) and Vol indicates blood volume (L) that are processed in a single collection. In our facility as well as many others, the most commonly processed blood volume for a single collection is 12 L, which usually takes about four hours. The collection goals can often be achieved with 12 L blood processing in healthy allogenic donors. Therefore, the first step is to determine whether a collection of 12 L blood processing can generate adequate CD34 cells. The prediction formula can be simplified to:

\[
\text{Predicted CD34 per kg of receipt BW (× 10^6/kg)} = \text{pre-CD34} \times k \times \left(\frac{\text{Donor BW/receipt BW}}{12}\right)
\]

(2)

If the predicted CD34 count is less than the target, it needs to be determined how long the collection should be extended with formula (1). As for the autologous donors, the formula can be simplified to:

\[
\text{Predicted CD34 (×10^6/kg)} = \text{pre-CD34} \times k \times \left(\frac{\text{Vol}/12}{12}\right)
\]

(3)

**Evaluation of the accuracy and utility of the PBSC prediction formula**

A good prediction can provide important information, especially for volunteer PBSC donations, because the collected PBSC product will be delivered to the recipient immediately after collection, before the number of CD34 cells become available. Whether the collection target is met therefore depends on the accuracy of the prediction. In this study, 45 volunteer donors underwent 12 L blood processing. Among them, 37 donors were predicted able to achieve the collection goal. Thirty four (92%) of these 37 donors actually achieved the goal, whereas 3 (8%) donors had a collected CD34 count below the target. Only one donor, however, had a significantly lower CD34 count than the target (38% lower than the target). In addition, nine donors were predicted to have a lower CD34 count than the target. Eight of these 9 donors had a final CD34 count lower than the target, which was consistent with the prediction results. One donor was predicted to have inadequate CD34 cells actually had enough CD34 cells.

**Correlation between collection efficiency and processed blood volume**

During PBSC collection, circulating CD34 cells were consistently removed from the peripheral circulation, followed by a dynamic re-equilibration of CD34 cells from bone marrow and other tissues.
The ratio between the collected CD34 cells and the pre-CD34 count reflects this mobilization process and was considered as the efficiency of collection procedure in this study. Moreover, although 12 L of blood has been used as a default volume to be processed regardless of donor’s body weight or total blood volume (TBV), the number of TBV processed in each collection varies. The relationship between the increase in circulating HSCs in the mobilization process and blood volume processing is complex and has not been depicted. For practical reasons, a linear relationship was assumed and a significant correlation between the collection efficiency and the number of TBV processed \( (r=0.70; \ p<0.001) \) was noted (Figure 2). This result supports the use of formula to determine the prolongation of leukapheresis in donors with inadequate pre-CD34 cells.

**Evaluation of CD34 cell prediction in extended PBSC collections**

We have shown the prediction can help to identify donors who need extended collection. In donors who underwent 12 L blood processing, the collected CD34 cells strongly correlated with the predicted CD34 cells \( (r=0.881; \ p<0.001) \) (Figure 3A). A similar correlation was observed in donors who needed an extended collection, although the correlation efficient was lower \( (r=0.618; \ p<0.01) \) (Figure 3B). When all the donations were included, the correlation efficient was 0.851 \( (p<0.001) \) (Figure 3C). Taken together, these results indicated that the prediction formulae cannot only accurately predict which donors need extended collection, but also provide a reliable estimation of how much the procedure should be extended in order to achieve collection goal.

**Achievement of collection goal vs. unnecessary extension of collection procedure**

The other important aspect of the collection prediction is to avoid excessive underestimation of CD34 cells in order to achieve the collection goal. Side effects associated with PBSC donation have been well recognized \[19\] and longer procedure been associated with increased donor complaints. In the present study, the number of donors whose CD34 yield was higher than predicted (underestimation) was almost the same as the number of donors whose CD34 yield was lower than predicted (overestimation) \( (48.6\% \ vs. \ 51.4\%) \) (Figure 4A). Overall, about 90\% of the predictions were correct regarding whether the collection could be achieved (Figure 4B). Among the 10\% of incorrect predictions, 6\% of donors were predicted as unable to achieve collection goal but they did. The rest of 4\% donors failed to achieve the collection goal because of overestimation of the CD34 cells. These results indicated that using the aforementioned formulae did not increase unnecessary extension of the PBSC collection procedures.

**Discussion**

More and more HSC transplantations employ PBSC donations. An important prerequisite for PBSC collection is an adequate response
Figure 4A: Evaluation of CD34 prediction accuracy. A: Underestimation means the CD34 cells were predicted low but the actual CD34 yield was higher. Overestimation means the CD34 cells were predicted high, but the actual CD34 yield was lower. The relative percentages of underestimation (red) and overestimation (blue) were shown.

Figure 4B: The percentage of correct prediction (blue) and incorrect prediction (purple) whether the collection goal will be achieved.

to bone marrow mobilization, which varies even in healthy allogeneic donors [20]. In the present study, as high as 50% of the healthy donors had a suboptimal pre-CD34 count that was considered incapable of meeting the collection targets with 12 L of blood processing. Thus, an accurate prediction method can help PBSC collecting facilities to determine the duration of the procedure before the completion of PBSC collection, which can improve the quality of patient care. Our goal is to provide an accurate, yet simple formula to estimate the PBSC count obtained prior to collection (pre-CD34) in estimation of total CD34 yield. The collection coefficient (k) relates to the skill and experience of apheresis staff, and we recommend other collecting facilities to modify the collection coefficient (k) by comparing the predicted value of CD34 cells to the real CD34 yield. In our facility, we use the formula first to identify donors who need extended collection. Next, we calculate the estimated blood volume needed to achieve the collection goal. The donors will be provided with this information, in order to make the decision whether to continue donation. If they choose to do so, they can opt to either undergo a prolonged collection or stop at 12 L of blood processing and come back the next day for another procedure. In our experience, most donors like to continue the procedure on the same day. It is the responsibility of collecting facility physicians to minimize donation-related discomforts. The most common complaints associated with the lengthy procedure include activity restriction on the donation bed/chair, restriction of arm movement when peripheral access is used, and symptoms caused by citrate toxicity including numbness, tingling, muscle cramping, hypotension and arrhythmia [21,22]. A good prediction method should therefore avoid underestimation of CD34 yield for the sake of increasing the chance to obtain adequate PBSCs. This will cause unnecessary prolongation of the procedure. The collecting facility should balance the task of collecting adequate PBSC with minimizing discomfort to the donors caused by the leukapheresis procedure. This can be achieved by adjusting the collection coefficient (k). With adaptation of a k of 0.85, we were able to equalize the underestimated predictions with overestimated predictions. At the same time, the collection goals were achieved in most cases.

In conclusion, we introduced a method to predict the PBSC yield collected by leukapheresis. The formulae are simple, yet able to accurately estimate the final yield without unnecessary prolongation of the procedures. This prediction method will help collecting facilities to perform PBSC collection efficiently and improve patient care.

References


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