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Rapid prediction of stem cell mobilization using volume and conductivity data from automated hematology analyzers

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Abstract

Background—Rapid analytics to predict circulating hematopoietic stem cells are valuable for optimal management of mobilization, particularly for the use of newer and costly mobilization agents such as plerixafor.

Study Design and Methods—We used step-wise, linear multiple regression modeling applied to cell population data collected by routine hematology analyzers (Beckman Coulter DxH 800) on patients undergoing autologous stem cell collection (n=131). Beta coefficients were used to derive a formula for a stem cell index (SCI). We then tested the correlation of SCI with stem cell counts and performance of the SCI as a predictor of poor mobilization with external validation in separate cohort (n=183).

Results—The SCI correlated strongly with CD34 counts by flow cytometry ($r = 0.8372$ in the development cohort, $r = 0.8332$ in the external validation cohort) and compares favorably with other rapid stem cell enumerating technologies. In the external validation cohort, the SCI performed well as a predictor (ROC AUC = 0.9336) of poor mobilization (CD34 count < 10), with a sensitivity of 72% and a specificity of 93%. When prevalence of poor mobilization was 33%, this resulted in a positive predictive value of 83% and a negative predictive value of 87%. The SCI also showed promise in tracking responses to plerixafor administration.

Conclusion—The findings demonstrate the utility of the cell population data collected by hematology analyzers to provide rapid data beyond standard CBCs, particularly for stem cell count prediction, requiring no additional reagents, specimen, or instrumentation.

Introduction

Hematopoietic stem cell transplantation (HSCT), including autologous transplantation, is a valuable therapeutic approach in the treatment of several diseases, most commonly in hematologic neoplasms, and particularly multiple myeloma, both early in therapy and at

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relapse [1, 2]. Several sources of hematopoietic stem cells (HSCs) may be used, including bone marrow harvest, peripheral blood derived stem cells, and potentially even *ex vivo* expanded or engineered precursors [3, 4]. While there is significant debate over the optimal source of HSCs and the relevant physiologic differences between them, peripheral blood derived HSCs collected by apheresis are an important and comparatively less-invasive approach to stem cell collection. HSCs are usually estimated using the surrogate surface marker CD34 measured by flow cytometry, and while the optimum dose is uncertain (and may be dependent on clinical scenario), a minimum dose of 2×10^6 CD34+ stem cells per kg is associated with successful and timely engraftment.

In order to collect adequate numbers of stem cells, HSCs must be mobilized into the peripheral circulation by stimulation with several agents including chemotherapeutics, G-CSF, and the CXCR4 antagonist plerixafor [5], among others. After mobilization, patients typically undergo a number of apheresis procedures to collect sufficient cells, often aiming to collect enough for multiple transplantations with cells cryopreserved for transplantation at a later date. In the United States, the most common mobilization regimens involve chemotherapy followed by cytokine therapy (usually G-CSF), or cytokine therapy alone [6]. Although chemotherapy prior to cytokine therapy improves yields, this method has unpredictable optimal timing of apheresis, in addition to concerns related to the chemotherapy itself, such as neutropenia. High rates of success have been achieved with peripheral blood stem cell collection, but patient responses to mobilization regimens are variable, and may depend on factors such as age, diagnosis, and prior therapy [7]. Estimates of mobilization failure with standard G-CSF regimens range from 10 to 40% of cases [5], which provided the impetus for newer agents such as the CXCR4 inhibitor plerixafor, and more recently VLA-4 inhibitors and the proteasome inhibitor bortezomib [8]. While plerixafor is highly effective at mobilizing stem cells, it remains costly (potentially exceeding \$6000 per dose) [9], and its use is complicated by a short half-life of approximately 3.6 hours with a maximum effect between 6–9 hours after subcutaneous injection [10]. These time restraints necessitate rapid and accurate HSC quantification for optimal and cost-effective use.

To maximize the efficiency and rates of success of HSC collection, the timing of apheresis is critical. Mobilization typically produces a transient peak in circulating HSCs such that efficiency of collection may vary greatly with respect to this timing. Most commonly, apheresis is initiated approximately 5 days after the start of G-CSF therapy, often alongside quantification of HSCs (based on CD34 positivity) in the peripheral blood by flow cytometry. Peripheral blood CD34+ stem cell counts measured by flow cytometry correlate well with collection yield [11]. However, flow cytometric measurements require specialized labs and may not be able to be performed at many centers given the technical expertise required. Furthermore, such measurements are relatively costly and time-consuming. The time-consuming nature limits the utility of flow cytometric quantification in real-time patient management. For example, although ‘just-in-time’ use of plerixafor in mobilization regimens has gained popularity for its efficacy and cost-effectiveness [12], same-day flow cytometric results may not be available and even less likely would results be available within the time frame of a clinic visit. As a convenient, rapid surrogate, some centers screen for adequate mobilization by tracking white blood cell (WBC) counts. However, WBC counts

correlate poorly with CD34+ counts [11] and the use of WBC to initiate apheresis risks poor cell yields and larger numbers of apheresis procedures that carry additional risks to the patient.

As an alternative to WBC counts, other commercial assays have been developed to predict stem cell counts, particularly HPC and XN-HPC enumeration offered by Sysmex analyzers. These analytics perform well ($R=0.88$ for XN-HPC in peripheral blood) in screening for adequate mobilization in peripheral blood, quantifying apheresis collections, and are already in use at several transplant centers [13, 14]. However, as these technologies are proprietary and not available at all centers, we wanted to investigate how data already collected by a commonly used standard hematology analyzer (Beckman Coulter DxH) could be exploited to derive stem cell predictors. Most commercial hematology analyzers collect a broad set of data (for Beckman Coulter systems, volume, conductivity, and scatter, often termed VCS parameters [15–17]) on the analyzed cells, only a fraction of which is used to provide the clinical CBC results, such as automated cell differentials. The additional data are termed “Cell Population Data” by Beckman Coulter, and others have assessed their value as predictors for conditions such as sepsis. In these systems, current impedance is used to measure cell volume and radiofrequency opacity is used to measure conductivity, a property that reflects internal composition of each cell. Recently, we and others explored the correlation of these parameters with stem cell counts to assess their potential to facilitate stem cell collection [18, 19]. Shin et al examined the correlation of individual parameters from similar instrumentation with harvest yields and found that several parameters showed significant correlation [18], while Golubeva et al showed a positive correlation between neutrophil cell population data and peripheral blood CD34 counts, suggesting utility in rapid CD34 estimation [20]. Building upon these findings, we examined the entire matrix of volume and conductivity cell population data from a Beckman Coulter instrument and performed multiple regression analysis to derive a rapid, quantitative model for predicting circulating stem cell counts.

Materials and Methods

Data Collection

All studies were performed at the Hospital of the University of Pennsylvania, Philadelphia, PA. All patients undergoing peripheral blood stem cell collection in our apheresis unit routinely have complete blood counts performed upon a pre-donation evaluation (usually the day prior to planned initiation of apheresis) and on each day of collection. In the present study, patients undergoing stem cell apheresis were monitored over a 2-year period and data collected under a planned quality assurance initiative. The day prior to initiation of apheresis, and on the morning of initial collection, peripheral blood samples were drawn into EDTA collection tubes for flow cytometric CD34 measurement (performed prior to initiation of apheresis) and CBCs (performed prior to and on each day of collection) which were performed on the Beckman Coulter DxH 800 hematology analyzer per standard operating procedures. CD34 cells were counted by standard flow cytometric ISHAGE protocols on a FACS Canto cytometer. Complete blood count and cell-population data from the DxH (48 variables per specimen) were exported into a data matrix with the corresponding flow

cytometric data. Additional data gathered included patient age, gender, diagnosis, and plerixafor use. Data were compiled into a deidentified database for further analysis.

Model Development and Data Analysis

Multiple linear regression analysis was performed using $\log_{10}(\text{peripheral CD34})$ as the dependent variable to reduce skewness and heteroscedasticity and 48 manufacturer pre-defined automated DxH variables (see Supplemental Table S1) as independent variables (SPSS, IBM, Armonk, NY). Individuals in the development cohort ($n=131$) were randomly selected into 10-fold subsets, and a model was derived using step-wise regression with a probability of entry of 0.05 and a probability of removal of 0.10 on each 90% subset. Four variables were included in at least 9 of the 10 model runs, which was our criteria for inclusion in our final model. The variables (as designated in the DxH software) were absolute neutrophil number (NEU#), standard deviation of the conductivity of early granulocytic cells (SD-C-EGC), mean of the conductivity of early granulocytic cells (MN-C-EGC), and the standard deviation of the conductivity of nucleated red blood cells (SD-C-NRBC). Although SD-C-NRBC met criteria for inclusion into the model, we noted that many patients did not have cells noted to be nucleated red blood cells by the automated counter, and flags associated with interferences or artifacts in this channel were frequent. Therefore, the final model included only NEU#, SD-C-EGC, and MN-C-EGC. To test the final model, we used the entry method with 10-fold internal cross-validation against each 10% excluded subset (see Supplemental Table S2). The beta coefficients in the final derived model were used to calculate a dimensionless “stem cell index” (SCI) that could be used to predict circulating stem cell counts. Our final formula for SCI was: $\text{SCI} = 10^{(0.015*(\text{NEU\#})+0.272*(\text{SD-C-EGC})-0.044*(\text{MN-C-EGC})+5.67)}$. The SCI was calculated by inputting each of the parameter values (as outputted by the analyzer) into an automated spreadsheet set up with the above formula. While the model was derived such that the SCI would mirror CD34 cells per μL , we choose to present the SCI as a dimensionless index to reflect the fact that it is not directly measuring cell numbers and is instead using an empiric calculation. We externally validated the SCI in an entirely separate cohort of 183 patients whose data were collected after development of the model. To analyze the ability of the SCI to predict when peripheral CD34 counts were $<10/\mu\text{L}$ (a clinically relevant threshold for initiation of stem cell collection) we calculated receiver-operator-characteristic curves using Prism (GraphPad, La Jolla, CA) and compared the performance of the SCI and white blood cell counts (WBC) as a control. ROC curves were compared using the method of Hanley and McNeil [21] and MedCalc software (MedCalc, Belgium).

Results

For the model development, 131 samples from 122 patients had complete data for inclusion into the computation. The median age was 60 (range 22–74) and patients were 55% male ($n=67$) / 45% female ($n=55$). The most common diagnosis was multiple myeloma ($n=91$, 69%), followed by non-Hodgkin lymphoma ($n=26$, 20%), Hodgkin lymphoma ($n=11$, 8%), amyloidosis ($n=2$, 2%), and germ cell tumor ($n=1$, 1%). The distribution of CD34+ peripheral blood counts at the pre-donation evaluation can be seen in Supplemental Figure 1, which demonstrates that 39% ($n=51$) of patients had a peripheral count of <10 CD34+

cell/uL, which may be predictive of insufficient yield on first harvest. In a subset of 54 patients in whom data on specific mobilization regimen was available, we found that 17 patients (31%) had plerixafor added to their mobilization regimen. All patients received G-CSF.

The multiple regression model was derived using the approach outlined in the Methods above (see Supporting Information for additional information) and identified three variables that were used to calculate the SCI: NEU#, SD-C-EGC, and MN-C-EGC. In the internal cross-validation, the median adjusted R^2 value of the model versus log-normalized CD34 was 0.6645 (range 0.647–0.697). Using the beta coefficients of this model to calculate the SCI, the Spearman r of the SCI versus untransformed CD34 count for the derivation set of 131 patients was 0.8372 (0.7753–0.8832 95% CI) (Figure 1). As a comparator, the WBC count was also assessed for its correlation with CD34+ stem cell count, as previous studies have demonstrated the relatively poor performance of this number as a predictor of mobilization [11]. The SCI correlated with peripheral CD34+ stem cell counts significantly better than WBC ($r = 0.6637$, 0.5518–0.7521 95%CI), although both were positively correlated with stem cell counts ($p < 0.0001$). Interestingly, there was an apparent sigmoidal response in CD34+ stem cell counts versus WBC. To evaluate the SCI in non-mobilized patient samples, 25 random samples from our hospital's central lab with normal WBC, RBC count, hemoglobin, and platelet counts were selected and analyzed for SCI. Clinical information for these samples was not available, but they are expected to approximate a non-mobilized population. The mean and median SCI in this population were 9 and 8, respectively.

We assessed the performance of the SCI as a rapid predictor of adequate mobilization ($CD34 > 10$ cell/uL) in the development cohort. This is a clinically relevant threshold as it can be utilized as a trigger for administration of plerixafor in a 'just-in-time' approach to mobilization. The performance of the SCI was assessed using receiver-operator-characteristic (ROC) curve analysis, with patients with $CD34 < 10$ as "positive" cases and patients with $CD34 > 10$ as controls. The area under the receiver-operator-characteristic curve for the SCI was 0.9206 (0.8711–0.9701 95%CI) (Figure 2). We found the SCI performed very well with a sensitivity of 76% (63–87% 95%CI) and a specificity of 91% (83–96% 95%CI) for predicting poor mobilizers at an SCI threshold of < 10 . In the development cohort (with 31% poor mobilizers), this corresponded to a positive predictive value of 85% and a negative predictive value of 86%. Using the WBC count to predict poor mobilizers, we found that at a predetermined threshold specificity of 91% (as to be equivalent to the SCI model), the WBC had a sensitivity of only 45% (31–60% 95%CI) at a cutoff of 17 (10^3 /uL). The apparently poor predictive ability of WBC at the decision point of CD34 of 10/uL likely reflects the fact that around this point there is a transition in the correlation to a relatively steep profile.

We then proceeded to further validate the correlation of the SCI with CD34 counts using an entirely external cohort. Data from 183 additional patients collected after derivation of the model were used for this purpose. Patients were all undergoing stem cell mobilization for autologous stem cell collection and transplant. While information regarding patient demographics and diagnosis was not collected in population, we expect the relative

composition of the external validation population to be similar to the development cohort as all data were collected in the same clinic population and no major changes in our population were seen over this time period. The external validation confirmed the correlation of the SCI with CD34 counts, with a Spearman r of 0.8332 (0.7811–0.8738 95%CI) for SCI versus peripheral CD34+ counts by flow cytometry (Figure 3). This was again significantly improved over the correlation of CD34 with WBC counts which showed $r=0.6842$ (0.5958–0.7563 95%CI). Test performance of SCI as a predictor of CD34<10 was very similar to the development cohort at 72% sensitivity (59–83% 95%CI), 93% specificity (86–96% 95%CI) at a threshold of SCI<10. Predictive values were 83% PPV, 87%NPV, with an area under the ROC curve of 0.9336 (0.8994–0.9677 95%CI). Test performance was significantly better than WBC as a predictor of adequate mobilization (area under ROC curve 0.8398, 0.7821–0.8975 95%CI). We found that setting the WBC cutoff at 17 (as previously determined) sensitivity was only 43% (30–56% 95%CI) with a specificity of 93% (87–97% 95%CI) (Figure 4). These analyses further validated the SCI parameter and demonstrated its superiority over WBC counts in an entirely separate cohort of patients.

Because the SCI measurement could be rapidly obtained and incurs no additional cost beyond routine CBCs, we were also interested in its ability to track stem cell counts repeatedly over time, particularly in real time on the day of stem cell collection in order to track responses to plerixafor administration. In a subset of patients mobilized with plerixafor and in whom data was available on the day prior to and the day of stem cell collection ($n = 17$), we assessed the response in SCI after administration of plerixafor. As we expected, all patients demonstrated an increase in SCI the morning following plerixafor (Figure 5). Furthermore, in patients who had a successful initial collection, defined as $>2 \times 10^6$ CD34+ cells/kg yield, there was a significant increase in SCI, while in those who failed initial collection ($<2 \times 10^6$ cells/kg), the increase in SCI was not significant.

Discussion

Peripheral blood CD34+ stem cells collected by apheresis are an important and comparatively convenient source of stem cells in hematopoietic stem cell transplantation, and potentially, a range of cell therapies. Because collection of stem cells from peripheral blood typically requires adequate mobilization from the bone marrow compartment, simple clinical tests for assessing mobilization have significant utility. Although enumeration of CD34+ stem cells from flow cytometry is a robust and well-validated approach for characterization of stem cell numbers, it is limited by cost, technical complexity, and turnaround time. In contrast, routine CBCs using automated hematology analyzers are ubiquitous, inexpensive, simple to perform, and offer ultra-rapid turnaround, with results as soon as minutes after specimen collection. If the latter technology could also be exploited for stem cell prediction, it would offer significant potential clinical benefit and actionable results, even within a given clinic visit.

In the present study, we aimed to use VCS parameters to develop a robust model to rapidly predict circulating stem cell counts such that these data could guide clinical management. We used multiple regression analyses to identify which variables could be informative in a linear model of peripheral stem cell count prediction, with CD34 counts by flow cytometry

as the reference standard. We found the absolute neutrophil count (NEU#) as well as two features of “early granulocytic cells”, the mean and standard deviation of their conductivity, were useful contributors to a stem cell prediction model. Others observed similar correlation of stem cells with conductance parameters of granulocytic cells [18], independently validating the present observations. Interestingly, the conductivity reflects internal complexity, and the mean conductivity was negatively correlated while the SD of the conductivity was positively correlated. We speculate that this suggests that the less overall complexity of the nuclear features and the wider their distribution, the more stem-cells will be circulating. This is consistent with expected morphology of immature hematopoietic cells, and validates the physiologic basis for the derived model. The generalizability of the SCI model to other hematology analyzers is uncertain. In a limited pilot study, we previously found that a different instrument (Beckman Coulter LH hematology analyzer) similarly showed correlation between some neutrophil CPD parameters and stem cell counts [22] (see Supplemental Figure S1). Therefore, we expect that similar empiric models should be able to be derived in other instruments which use volume and conductivity measurements.

This model was used to calculate a predictive score we termed the stem cell index (SCI). The SCI proposed in this study utilizes data collected in routine CBC analyses, requiring no additional cost beyond tests that are usually routinely performed and no additional specimens beyond those routinely collected. We propose that the SCI can be used for real-time management of stem cell collection using an algorithm such as the one outlined in Figure 6, which is greatly facilitated by the rapid turn-around time for SCI measurement. No additional equipment or proprietary reagents are necessary. The model performs similarly to commercially available platforms such as the HPC enumeration offered by Sysmex [13], and is similarly ultra-rapid, with results available within minutes. While data in a subset of the present cohort suggest that SCI can be used to monitor response to plerixafor, the number of patients in whom data was available for SCI calculation both pre- and post-plerixafor was limited, and a larger study would be necessary to confirm the utility of SCI in this setting. In 2013, we performed a small validation study of HPC (n=32) on a similar population of patients undergoing autologous stem cell collection using a Sysmex XE5000, and found a lesser ability to predict poor (CD34<10) mobilization (AUC=0.7727, Supplemental Figure S2). However, it is important to note that recent advances have significantly improved the performance of the HPC technology [13]. Given the test-performance findings and the advantageous features of SCI measurement, we propose that the SCI can be used as a threshold for initiating stem cell apheresis and guidance of administration of additional mobilization agents such as plerixafor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

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