Title
Factors influencing platelet clumping during peripheral blood hematopoietic stem cell collection.

Journal
Transfusion, 57(5)

ISSN
0041-1132

Authors
Mathur, Gagan
Mott, Sarah L
Collins, Laura
et al.

Publication Date
2017-05-01

DOI
10.1111/trf.14022

Peer reviewed

Published in final edited form as:

Transfusion. 2017 May ; 57(5): 1142–1151. doi:10.1111/trf.14022.

Factors influencing platelet clumping during peripheral blood hematopoietic stem cell collection

Gagan Mathur[1], **Sarah L. Bell**[2], **Laura Collins**[1], **Gail A. Nelson**[1], **C. Michael Knudson**[1], and **Annette J. Schlueter**[1]

[1]Department of Pathology, University of Iowa, Iowa City, Iowa

[2]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, Iowa

Abstract

BACKGROUND—Platelet clumping is a common occurrence during peripheral blood hematopoietic stem cell (HSC) collection using the Spectra Optia mononuclear cell (MNC) protocol. If clumping persists, it may prevent continuation of the collection and interfere with proper MNC separation. This study is the first to report the incidence of clumping, identify precollection factors associated with platelet clumping, and describe the degree to which platelet clumping interferes with HSC product yield.

STUDY DESIGN AND METHODS—In total, 258 HSC collections performed on 116 patients using the Optia MNC protocol were reviewed. Collections utilized heparin in anticoagulant citrate dextrose to facilitate large-volume leukapheresis. Linear and logistic regression models were utilized to determine which precollection factors were predictive of platelet clumping and whether clumping was associated with product yield or collection efficiency.

RESULTS—Platelet clumping was observed in 63% of collections. Multivariable analysis revealed that a lower white blood cell count was an independent predictor of clumping occurrence. Chemotherapy mobilization and a lower peripheral blood CD34+ cell count were predictors of the degree of clumping. Procedures with clumping had higher collection efficiency but lower blood volume processed on average, resulting in no difference in collection yields. Citrate toxicity did not correlate with clumping.

CONCLUSION—Although platelet clumping is a common technical problem seen during HSC collection, the total CD34+ cell-collection yields were not affected by clumping. WBC count, mobilization approach, and peripheral blood CD34+ cell count can help predict clumping and potentially drive interventions to proactively manage clumping.

Hematopoietic stem cell (HSC) transplantation is part of standard therapy for many hematologic cancers.[1] Peripheral blood (PB) HSC col lection using apheresis has mostly

Address reprint requests to: Annette J. Schlueter, Department of Pathology, University of Iowa, 200 Hawkins Drive, C250 GH, Iowa City, IA 52242; annette-schlueter@uiowa.edu.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website.

CONFLICT OF INTEREST

The authors had no conflicts of interest to disclose.

replaced bone marrow (BM) as a source of HSC for autologous transplants.[2] Patients are mobilized by chemotherapy and/or cytokines to stimulate the production and release of HSC from BM.[3,4] Current evidence suggests that higher stem cell doses reduce the time to engraftment and improve transplantation outcomes.[5] To support this, it is important to optimize the stem cell yield, which is the total number of HSCs collected and the collection efficiency (CE), which is the percentage of HSCs going through the apheresis device that is collected into the HSC product. The yield and CE are affected by both patient-specific and technical collection-specific factors.[6–8] In addition, technical problems during collection, such as difficulty with venous access, difficulty maintaining a stable interface, platelet clumping, etc., may slow the collection and reduce the HSC yield by decreasing the amount of blood processed.

Platelet clumping has been noted[9] during HSC collection using the mononuclear cell (MNC) collection protocol on the Spectra Optia (Terumo BCT, Lakewood, CO). Platelet clumps, when present, are seen traveling through the collect port in the connector.[10,11] Many factors, such as patients' underlying disease, mobilization regimen, blood contact with artificial surface, and centrifugal speed of the instrument, can contribute to platelet clumping in apheresis systems.[12–14] Potential patient-specific factors include the production of procoagulant proteins and high levels of inflammatory cytokines in patients with myeloma[12] as well as the increased thrombin generation and fibrin formation seen in healthy donors who received filgrastim mobilization.[13] In addition, our hypothesis is that young, large platelets from recovering/regenerating hematopoietic systems (mainly chemotherapy mobilization) are more likely to be activated and might lead to clumping in the apheresis system during collection. Interestingly, platelet clumping was not observed as a significant problem in the COBE Spectra (Terumo BCT) compared with the Spectra Optia, possibly because of relatively lower centrifugal speed and larger filter pores in the return reservoir.[14]

Platelet clumping could affect CE by interfering with proper separation in the channel connector and/or in the chamber. In addition, excessive clumping can interfere with the proper function of the reservoir. If the low-level reservoir sensor becomes obstructed and cannot function properly, then the system cannot adequately manage the patient's fluid balance. If the filter becomes completely occluded, then the reservoir cannot be emptied, and the run must be discontinued.[10,11]

Terumo BCT identifies this problem and recommends decreasing the whole blood:anticoagulant (WB:AC) ratio to resolve platelet clumping.[10,11] Increasing the amount of AC can help prevent platelet clump formation, but the use of more AC increases the possibility of citrate reaction.[15,16] This is particularly a problem with HSC collections in which large volumes of blood are processed due to the long run time required. If platelet clumping persists, then it may lead to clotting in the system, which is difficult, and sometimes impossible, to eliminate. Terumo BCT also states that it is difficult to predict clumping, because it does not depend on the platelet count and varies between patients.[10,11]

In our experience, platelet clumping was frequently observed with Spectra Optia during HSC collections using the MNC protocol, necessitating alterations to the standard HSC collection parameters. We are unaware of any studies addressing the incidence of platelet

clumping or risk factors that predict its occurrence during HSC collection by apheresis. In this retrospective study, the incidence of platelet clumping during HSC collection using the MNC protocol on the Spectra Optia was determined. In addition, patient-related and collection-related factors were examined to determine their association with the incidence and degree of platelet clumping. Finally, the influence of platelet clumping on apheresis run parameters and product CD34+ cell content was evaluated.

PATIENTS AND METHODS

Patient population

A retrospective chart review was conducted on 298 consecutive HSC collections performed on 128 adult patients at the DeGowin Blood Center, University of Iowa Health-care, using the MNC protocol on Spectra Optia, from February 2014 to September 2015. Laboratory and clinical data from the patient, as well as HSC collection parameters and product data, were obtained and correlated with the platelet clumping observed during the collection. This project was reviewed by the University of Iowa Institutional Review Board (IRB) and was approved under IRB-01.

Stem cell mobilization

The patients with malignant plasma cell disorders were primarily mobilized with combined dexamethasone/cisplatin/doxorubicin/cyclophosphamide/etoposide (D-PACE) or similar chemotherapy regimen, with cytokines (filgrastim with or without plerixafor) occasionally added during count recovery for patients who were slow to mobilize. If a patient required cytokines in addition to chemotherapy to mobilize, then they were classified in the chemotherapy mobilization group. Patients with lymphoma and a few patients with malignant plasma cell disorders were mobilized with cytokines alone.

Chemotherapy-mobilized patients underwent HSC collection after recovery of hematopoiesis. When the white blood cell count (WBC) exceeded 1000/μL after the nadir from chemotherapy (generally about Day +13), hematopoietic progenitor cell (HPC) and/or PB CD34+ cell measurement began to determine whether the patient was ready to begin PB stem cell (PBSC) collection. If HSC collection did not begin by Day +15 postchemotherapy, then the patient began receiving 5 μg/kg filgrastim twice daily until collections were complete. If HSC collection did not begin by Day +17, then 24 mg plerixafor was given on the evening prior to anticipated collection (the dose was reduced by 50% if creatinine clearance was <50 mL/minute) and was continued until collections were complete. HPC counts ≥7/μL or PB CD34+ cell counts ≥10 CD34+ cells/μL resulted in the initiation of PBSC col lection for chemotherapy-mobilized patients.

Cytokine-mobilized patients received 10 μg/kg/day filgrastim starting 4 days before collection and continuing until PBSC collections were complete. Some patients received plerixafor (at the same dosing as chemotherapy-mobilized patients) on the evening before each PBSC collection based on their HPC and/or PB CD34+ cell counts. Patients who had HPC counts ≤0.5/μL or PB CD34+ cell counts ≤10 CD34+ cells/μL received plerixafor administration before PBSC collection as described previously.[17]

PBSC collection

Collections were performed using the Spectra Optia MNC protocol (Terumo BCT) with AC citrate dextrose (ACD-A) containing heparin (6 units heparin/mL ACD-A) to allow for large-volume collections while minimizing the risk of citrate reactions. In general, the collection was stopped when 30 L of WB was processed or after a 5-hour run time, whichever occurred first. Central venous access was used if peripheral access was not possible or was not preferred by the donor. The collections were performed at maximum draw speed of 100 mL/minute for peripheral venous access and 125 mL/minute for central venous access. Measures taken to mitigate symptoms of citrate toxicity (tingling, numbness, cramping) included slowing the WB flow rate and calcium supplementation with milk products or calcium carbonate. In the event of severe cramping, intravenous calcium gluconate was administered. No prophylactic calcium was administered intravenously during collections.

Eighty milligrams of aspirin was given prophylactically to mitigate platelet clumping if the platelet count was ≥80,000/μL. The collect port was vigilantly monitored for the appearance of platelet clumps, which were recorded in the nursing procedure note. These were identified as a dark mass, which could be light on either side, traveling through the collect port in the channel connector. Difficulty with establishing and maintaining the interface was also considered a sign of platelet clumping.

Data collection

Medical records of study patients were retrospectively reviewed to obtain laboratory and clinical data as well as HSC collection parameters and HSC product information. The clinical data collected included demographic information, diagnosis, mobilization approach, platelet transfusions received in the 24 hours preceding HSC collection, and preprocedure laboratory values related to the collection (WBC, platelet, HPC, and PB CD34+ cell counts and mean platelet volume [MPV]). The collection details evaluated included total blood volume (TBV) processed, CE, minimum WB:AC ratio used, maximum WB flow rates, and citrate toxicity. CE was calculated as follows: CE = total CD34+ cells in the HSC product/(mL TBV processed × preprocedure PB CD34+ cells/μL × 1000). The default WB:AC ratio used to initiate collections was 26:1. If clumping was noted during collection, then the WB:AC ratio was decreased gradually until clumping disappeared. Therefore, a lower WB:AC ratio suggested more severe platelet clumping. The minimum WB:AC ratio used during a procedure was selected for evaluation. Collections with minimum ratios of 26:1 were classified as no clumping, ratios from 24:1 to 19:1 were classified as mild clumping, ratios from 18:1 to 13:1 were classified as moderate clumping, and ratios <13:1 were classified as severe clumping. To facilitate certain data analyses, WB:AC ratios were converted to ordinal values, e.g., a WB:AC ratio of 26:1 was converted to 26.

Exclusions

Seven collections from four patients with solid organ tumors (Ewing’s sarcoma, metastatic teratoma, testicular cancer) were excluded because of the small sample size of patients with these diagnoses. Eleven collections from eight allogeneic donors were also excluded due to the small number of these donors in the data set. One patient had collections during two

distinct time periods, and collections from the second time period were excluded (three collections). Two collections were excluded because of substantial technical difficulties (flow rate and pressure alarms, which were determined to be unrelated to platelet clumping). Seventeen collections in 15 patients were excluded because the clumping reported and the WB:AC ratio used did not correspond.

Statistical analysis

To determine which factors were predictive of occurrence and the degree of platelet clumping, in addition to whether clumping was associated with TBV processed or product yield, linear and logistic regression models using generalized estimating equations were applied. Visual inspection of variable distributions was performed to identify potential extreme outliers. Of the few outliers identified, all were attributable to data entry errors and were corrected. Tests for normality were not performed. An exchangeable correlation structure was used to model the possible dependency among repeated measurements within a patient. Variables that were significant at the univariable level were included in the multivariable models, with the exception of the HPC count (due to the higher degree of missing information, because the HPC count was not systematically performed on each collection day). Estimated effects of predictors are reported as β coefficients or odds ratios along with 95% confidence intervals. Analyses were initially conducted across all patients and collections in the final data set. Because chemotherapy-mobilized patients were just recovering BM function at the time of collection, whereas patients with lymphoma had recovered their PB counts several weeks before collection, the influence of precollection factors on the incidence and degree of platelet clumping were also further analyzed by mobilization type. All statistical testing was two-sided and was assessed for significance at the 5% level using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Data from 258 HSC collections performed for autologous transplantation on 116 patients were available for analysis. Patient demographics are shown in Table 1. The detailed indications for transplantation and mobilization regimens are shown in the online supporting information (Tables S1 and S2). Laboratory values of the patients obtained on the day of collection just before apheresis are shown in Table 2. The median number of collections per patient was 2 (range, 1-6 collections per patient). Platelet clumping was observed in 63% of collections.

Identification of factors associated with the presence of platelet clumping

Univariable analysis of patient-related factors revealed that chemotherapy-mobilized patients are at 1.98 times increased odds of having measurable platelet clumping during collection ($p = 0.02$) compared with cytokine-mobilized patients (Fig. 1, top). With each 1000/μL increase in the WBC count, 1/μL increase in the HPC count, and 1/μL increase in the CD34+ cell count, the odds of platelet clumping during collection decreased significantly by 2%, 4%, and 1%, respectively.

Upon multivariable analysis, only the WBC count was identified as an independent predictor of platelet clumping after adjustment for mobilization. With each 1000/μL increase in the WBC count, the odds of platelet clumping decreased by 3% (Fig. 1, bottom). (In addition, there was a trend toward significance for a lower CD34+ cell count as a predictor of increased clumping.) Figure 2 further illustrates that, as the WBC count increases, the incidence of platelet clumping decreases.

On univariable analysis of the subgroup of chemotherapy-mobilized patients, lower WBC, HPC, and CD34+ cell counts again were identified as significantly associated with platelet clumping (Fig. 3, top). With each 1000/μL increase in the WBC count, 1/μL increase the in HPC count, and 1/μL increase in the CD34+ cell count, the odds of platelet clumping during collection decreased significantly by 4%, 8%, and 2%, respectively. Both the WBC count and the CD34+ cell count continued to be significant predictors of platelet clumping on multivariable analysis (Fig. 3, bottom). With each 1000/μL increase in the WBC count and 1/μL increase in the CD34+ cell count, the odds of platelet clumping decreased by 4% and 1%, respectively. No significant associations were identified for cytokine-mobilized patients, including whether or not plerixafor was part of the mobilization regimen (data not shown).

As a group, the significant predictors of platelet clumping indicated that clumping was most likely to occur in the first collections that take place as hematopoiesis recovers from myelosuppressive chemotherapy (lower WBC, HPC, and PB CD34+ cell counts). These data supported a hypothesis that younger, larger platelets coming out of the regenerating BM are more functionally active and might contribute to clumping.[18,19] If this were true, then platelet transfusion shortly before HSC collection might mitigate the problem (i.e., having a higher fraction of mature platelets in the circulation might limit clumping). In an attempt to address this hypothesis, this parameter was evaluated. However, only 15 patients had received at least 1 platelet transfusion within the 24 hours before HSC collection, involving 36 total collections. This data set was underpowered to detect a significant difference between the groups, and no obvious trends were identified between platelet transfusions and clumping. Because aspirin was routinely given to patients who had platelet counts ≥80,000/μL, this medication could not be evaluated as an independent predictor of platelet clumping.

Predictors of the degree of platelet clumping

To estimate the degree or severity of platelet clumping in a collection, the WB:AC ratio used for the collection was evaluated. A lower WB:AC ratio (relatively more AC) indicated that more clumping was observed and required more AC. The lowest WB:AC ratio used during a procedure was recorded for this evaluation. Univariable analysis showed that, in patients with plasma cell disorders, the WB:AC ratio was significantly lower than that in patients with lymphoma (Fig. 4, top). The average WB:AC ratio for patients with lymphoma was 22.48; whereas, for patients with plasma cell disorders, it was 16.52. Similarly, in chemotherapy-mobilized patients, the WB:AC ratio was significantly lower than that in patients who were mobilized with cytokines ($p < 0.01$). The average WB:AC ratio for chemotherapy-mobilized patients was 16.06; whereas, for cytokine-mobilized patients, it was 22.13. Lower WBC, HPC, PB CD34+ cell, and platelet counts and MPV were significantly associated with a higher degree of platelet clumping. On multivariable analysis,

only the type of mobilization and the PB CD34+ cell count were identified as independent predictors of the degree of platelet clumping (Fig. 4, bottom).

In the subgroup of chemotherapy-mobilized patients, univariable analysis found that only the HPC and CD34+ cell counts were significantly associated with degree of platelet clumping (Fig. 5). For cytokine-mobilized patients, only age was significantly associated with degree of platelet clumping. For every 5-year increase in age, the WB:AC ratio was higher, on average, by 0.39 ($p = 0.02$). Overall, other than the association of age with less platelet clumping in cytokine-mobilized patients, the variables that were associated with degree of platelet clumping were quite similar to those associated with incidence of platelet clumping.

Impact of presence of platelet clumping on apheresis run parameters, patient adverse events, and HSC product CD34+ cell content

Because platelet clumping can necessitate multiple adjustments to the baseline apheresis instrument settings to avoid irreversible clotting in the collection set, it was of interest to determine whether run parameters required adjustment that ultimately would increase adverse reactions in the patient or decrease CE or HSC product CD34+ cell yield. Apheresis collection parameters and associated patient characteristics are shown in Table 3. No collections were terminated early (<5-hour run time) because of the inability to maintain blood flow in the apheresis set due to platelet clumping. However, the TBV processed and the CE were significantly affected by clumping. Based on a statistical model in which the correlation within a subject (e.g., repeated measurements) was partitioned out, on average, the TBV processed was 1678 mL lower, and the CE was 11.4% higher ($p < 0.01$) for collections in which clumping was present than for collections in which no clumping was noted. The CD34+ cells collected in the HSC product, the maximum WB flow rate, and the degree of citrate toxicity were not significantly affected by the presence or absence of platelet clumping. No moderate or severe adverse events unrelated to citrate toxicity were noted during the HSC collections.

The 15 collections that had very low TBV processed (<15 liters) were analyzed separately to assess the degree to which clumping contributed to the very low TBV. In 7 of these collections, the run time was less than 5 hours, because the procedure was started later in the day (4 collections) or the patient had nearly reached the collection goal the previous day (3 collections). In all of the remaining collections, severe clumping was either noted in that collection, or the procedure was run with large amounts of AC because of severe clumping in a previous collection, and this necessitated a slower WB flow rate.

DISCUSSION

Platelet clumping is commonly seen during HSC collection using the MNC protocol on Spectra Optia. The goal of this study was to document the incidence of platelet clumping during these collections, evaluate its impact on patient adverse events and product HSC yield, and identify factors associated with platelet clumping. Identification of these factors would potentially allow prediction and proactive management of clumping to ultimately improve patient safety during collection as well as product quality. The incidence of platelet

clumping was quite high in our study population (63%), necessitating frequent changes to standard collection parameters, including WB:AC ratios.

On univariable analysis, chemotherapy-mobilized patients had a significantly increased incidence and degree of clumping compared with cytokine-mobilized patients. Similarly, patients with a diagnosis of plasma cell disorder had a trend toward increased incidence of platelet clumping versus those with a lymphoma diagnosis ($p = 0.06$), and patients with plasma cell disorder were significantly more likely to require a lower WB:AC ratio. The diagnosis and mobilization in the patients from this study were tightly linked, because most patients who had plasma cell disorders (91%) were mobilized with chemotherapy. Therefore, diagnosis was excluded as a variable when performing multivariable analysis.

In multivariable analysis, only an increased preprocedure WBC count was significantly associated with a decreased incidence of clumping in the entire study group. Within the group of patients who were chemotherapy-mobilized, both increased WBC and CD34+ cell counts were significantly associated with decreased platelet clumping. A decreased degree of platelet clumping was significantly associated with an increased CD34+ cell count in the entire study group. Overall, these findings suggest that patients who have hematopoietic systems that are just recovering from chemotherapy or are less responsive to cytokine mobilization are more likely to experience platelet clumping in their HSC collections. Patients who had a higher WBC count also tended to have a higher platelet count (data not shown). A higher platelet count increases the collect pump rate, which moves cells through the collect port faster. It is possible that the faster flow rate through this line limits the ability of the platelets to clump.

It is interesting that platelet count was not a statistically significant predictor of incidence or degree of platelet clumping. Aspirin administration to virtually all patients who had platelet counts ≥80,000/μL may have limited platelet clumping in this group, thus obscuring a true relationship between platelet count and clumping. (However, a prior study found no difference in the frequency of platelet clumping during apheresis using ACD-A/heparin AC between patients who were taking aspirin and those who were not.[14])

Our hypothesis was that young, large platelets might be responsible for the clumping observed during the collection. Higher MPV was not significantly associated with the incidence of platelet clumping, but it was significantly associated with the degree of platelet clumping in univariable analysis of the overall population. Young platelets are also more easily activated in the presence or absence of agonists,[20] and it remains possible that this characteristic might at least partially explain the associations found in this study. Unfortunately, immature platelet fraction measurements were not available for the patients in this study.

When analyzing the impact of clumping on apheresis run parameters, clumping was associated with significantly smaller TBV processed but increased CE. The reason why CE was higher when clumping was observed is unclear. This finding may initially suggest that platelet clumping is a desired finding during stem cell collection. However, the CD34+ cell yield in HSC products was not significantly different between procedures where clumping

was observed and those where it was not observed. Patients who showed clumping had lower PB CD34+ cell counts as well as significantly lower TBV processed. Based on the CE equation, both PB CD34+ cell count and TBV processed are inversely proportional to CE and may explain why higher CEs were observed in collections where clumping occurred. The third parameter in the CE equation, CD34+ cell yield in HSC products (directly proportional to CE), was constant (not significantly different between procedures where clumping was observed and those where it was not observed). Thus, it can be inferred that the increased CE seen in collections with clumping did not necessarily result in a better collection. If there had been no platelet clumping in a particular collection, then perhaps the ability to process a higher TBV could have led to a larger yield of CD34+ cells in the HSC product. Thus platelet clumping is not necessarily a desirable characteristic of a stem cell collection.

There are several limitations to this study. First, the study population uniformly underwent collection using the MNC protocol on Spectra Optia, and the AC used for the collections was ACD-A with heparin. This combination of parameters has been previously reported to result in platelet clumping[9] (although, in our experience, no procedures necessitated conversion to heparin-free ACD-A to complete the collection). Thus, our results may overestimate the incidence of clumping in apheresis collections on other platforms or with ACD-A AC without heparin and do not allow the evaluation of heparin's role (if any) on collection instrumentation in platelet clumping. In addition, the goal for all collections was to perform large-volume leukapheresis (30 liters or 5 hours). No data are available to assess the frequency or severity of platelet clumping or the impact on collection parameters/outcomes when other WB volume processing targets are used. Finally, HSC collections performed on healthy allogenic donors and autologous collections for patients with solid organ tumors were excluded because of small sample sizes; therefore, the applicability of the findings in this study to collections from these types of patients/donors cannot be readily assessed. Moderate-to-severe clumping was observed in 2 of the 11 collections from allogeneic donors who were excluded from formal analysis in our patient cohort. Thus platelet clumping remains a possibility during stem cell collections even in healthy donors.

In conclusion, for the first time, this study quantitates a high rate of platelet clumping during Optia MNC procedures that utilized heparin in the AC. In addition, the type of HSC mobilization and PB parameters associated with early BM recovery from chemotherapy are predictors of platelet clumping. Patients who are mobilized with chemotherapy, particularly when collected with a low WBC, are more likely to show clumping during HSC collection and could potentially be proactively managed to prevent clumping from having a deleterious effect on the collection. For example, their procedures could be initiated with a lower WB:AC ratio. Fortunately, the HSC yield from collections was not significantly decreased by platelet clumping, and WB:AC adjustments made in response to clumping did not lead to an increase in citrate reactions. It remains possible that platelet function might play a role in clumping during HSC collection, and further studies are needed to address its possible role.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Beth Alden for providing data on HSC products and Heather Fleming for secretarial assistance with manuscript submission.

This study was supported by the Department of Pathology, University of Iowa.

ABBREVIATIONS

AC	anticoagulant
CE	collection efficiency
E-PACE	combined dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide
HPC	hematopoietic progenitor cell
MNCs	mononuclear cells
MPV	mean platelet volume
TBV	total blood volume.

References

1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006; 354:1813–26. [PubMed: 16641398]
2. Schmitz N, Dreger P, Linch D, et al. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet. 1996; 347:353–7. [PubMed: 8598700]
3. Petit I, Szyper-Kravitz M, Nagler A, et al. G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. Nat Immunol. 2002; 3:687–94. [PubMed: 12068293]
4. Schwartzberg LS, Birch R, Hazelton B, et al. Peripheral blood stem cell mobilization by chemotherapy with and without recombinant human granulocyte colony-stimulating factor. J Hematother. 1992; 1:317–27. [PubMed: 1285381]
5. Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant. 2014; 20:295–308. [PubMed: 24141007]
6. Gidron A, Verma A, Doyle M, et al. Can the stem cell mobilization technique influence cd34+ cell collection efficiency of leukapheresis procedures in patients with hematologic malignancies? Bone Marrow Transplant. 2005; 35:243–6. [PubMed: 15580281]
7. Koumakis G, Vassilomanolakis M, Hatzichristou H, et al. Predictive factors affecting mobilization and peripheral blood stem cell (PBSC) collection using single apheresis (SA) for rescuing patients after high-dose chemotherapy (HD.CHE) in various malignancies. Bone Marrow Transplant. 1996; 18:1065–72. [PubMed: 8971374]
8. Ikeda K, Kozuka T, Harada M. Factors for PBPC collection efficiency and collection predictors. Transfus Apher Sci. 2004; 31:245–59. [PubMed: 15556472]
9. Burgstaler E, Winters J. Comparison of 3 anticoagulant techniques used during hematopoietic progenitor cell collection using the Terumo BCT Spectra Optia. J Clin Apher. 2015; 30:64–5.
10. Terumo BCT. Operator's manual, Spectra Optia® apheresis system. Lakewood (CO): Terumo BCT; 2015.
11. Terumo BCT. Mononuclear cell collection student handbook, Spectra Optia® apheresis system. Lakewood (CO): Terumo BCT; 2013.

12. Politi P, Durazzi SM, Picardi F. Thrombotic risk in patients undergoing peripheral stem cell apheresis and low-molecular weight heparin prophylaxis pre-apheresis. Transfus Apher Sci. 2012; 47:229–34. [PubMed: 22842110]
13. Canales MA, Arrieta R, Gomez-Rioja R, Diez J, Jimenez-Yuste V, Hernandez-Navarro F. Induction of hypercoagulability state and endothelial cell activation by granulocyte colony-stimulating factor in peripheral blood stem cell donors. J Hematother Stem Cell Res. 2002; 11:675–81. [PubMed: 12201956]
14. Handschel D, Etienne Janssens M, Gericke M, De Reys S, Borberg H. Comparative evaluation of a heparin-citrate anti-coagulation for LDL-apheresis in two primary apheresis systems [published online ahead of print 2016 Sep 27]. J Clin Apher.
15. Hegde V, Setia R, Soni S, et al. Prophylactic low dose continuous calcium infusion during peripheral blood stem cell (PBSC) collections to reduce citrate related toxicity. Transfus Apher Sci. 2016; 54:373–6. [PubMed: 26915952]
16. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the national marrow donor program. Blood. 2009; 113:3604–11. [PubMed: 19190248]
17. Steussy B, Capper M, Krasowski M, et al. Algorithms utilizing peripheral blood hematopoietic progenitor cell counts in lieu of some cd34+ cell counts predict successful peripheral blood stem cell collections with substantial time and cost savings. ISBT Sci Ser. In press.
18. Karpatkin S. Heterogeneity of human platelets. I. Metabolic and kinetic evidence suggestive of young and old platelets. J Clin Invest. 1969; 48:1073–82. [PubMed: 5771188]
19. Karpatkin S. Heterogeneity of human platelets. II. Functional evidence suggestive of young and old platelets. J Clin Invest. 1969; 48:1083–7. [PubMed: 5771189]
20. Schneider DJ, Chava S. Factors influencing platelet reactivity in patients undergoing coronary artery bypass surgery. Coron Artery Dis. 2016; 27:185–90. [PubMed: 26751426]

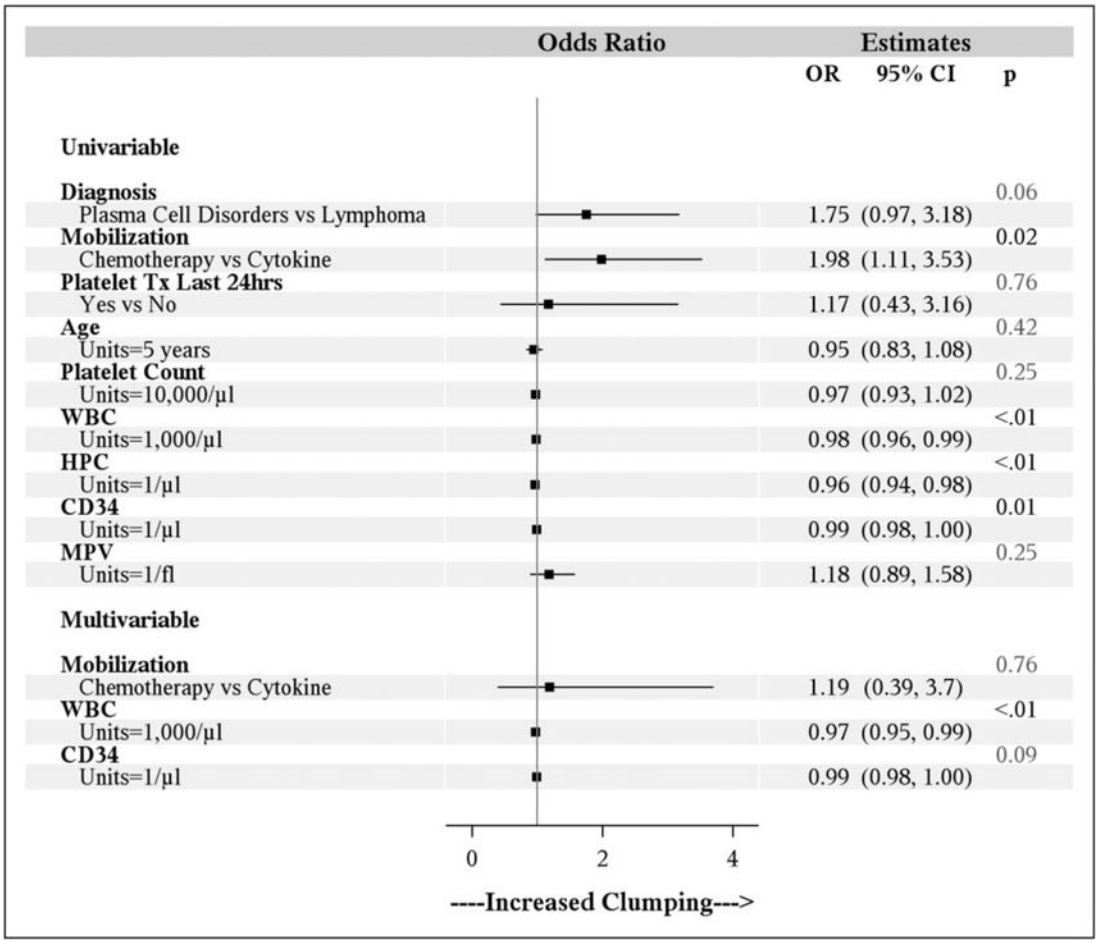

Fig. 1.

Univariable and multivariable analyses of associations between precollection factors and the presence of platelet clumping in the entire study population. OR = odds ratio; CI = confidence interval; Tx = treatment; WBC = white blood cells; HPC = hematopoietic progenitor cells; MPV = mean platelet volume.

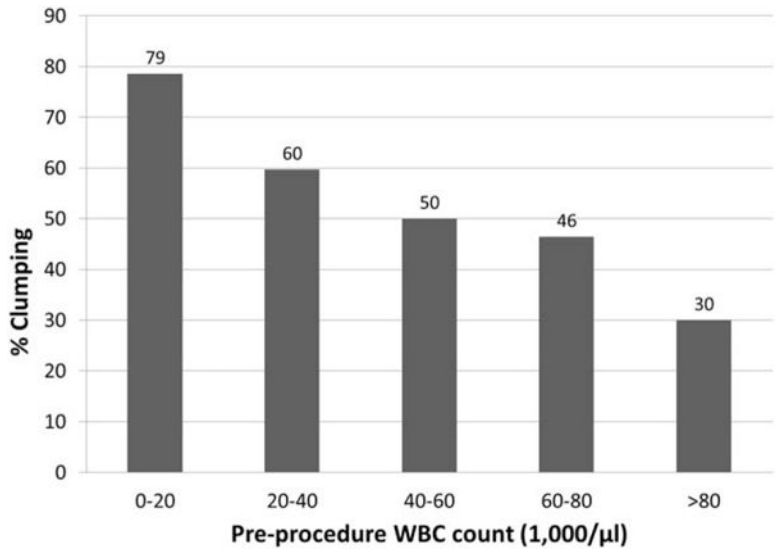

Fig. 2.

Rate of clumping at different levels of white blood cell (WBC) counts. Numbers on top of each bar are the mean clumping rate for each group.

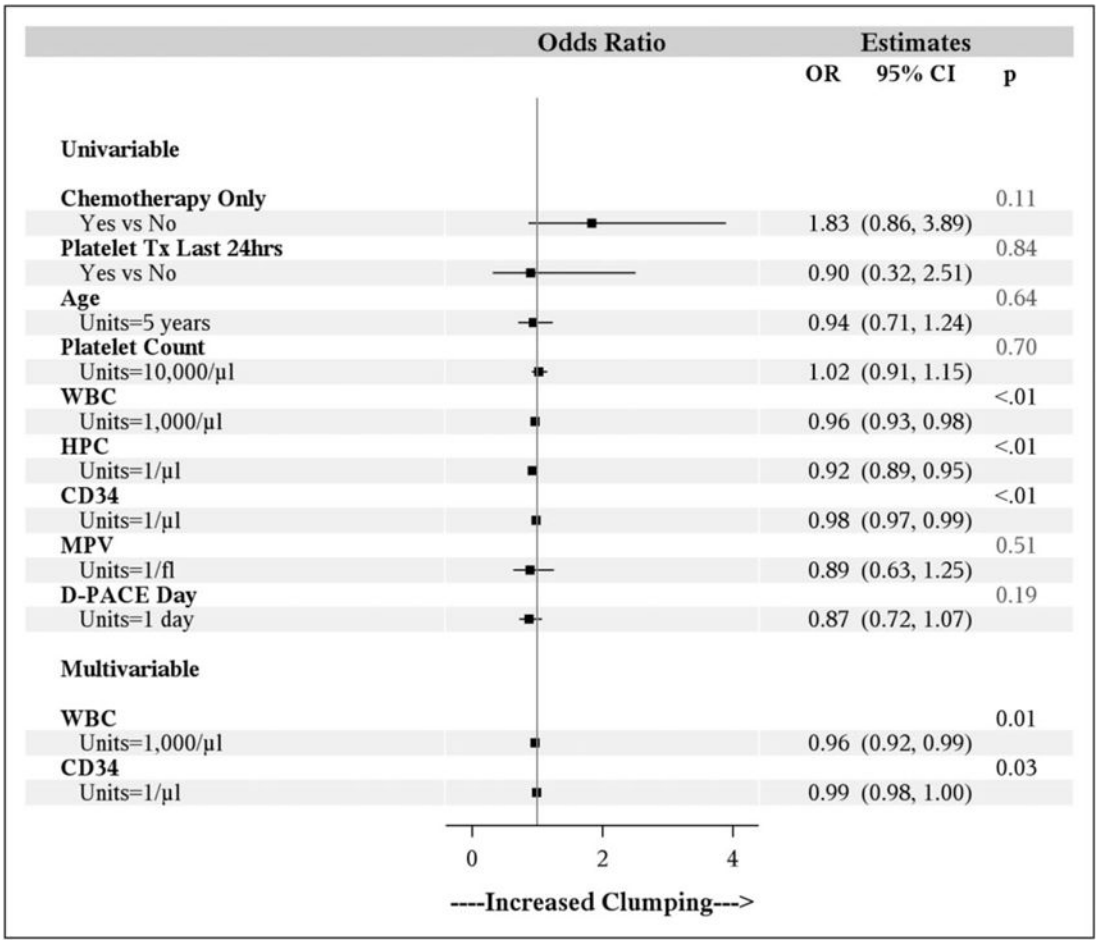

Fig. 3.

Univariable and multivariable analyses of associations between precollection factors and the presence of platelet clumping in the chemotherapy-mobilized subgroup. OR = odds ratio; CI = confidence interval; Tx = treatment; WBC = white blood cells; HPC = hematopoietic progenitor cells; MPV = mean platelet volume; E-PACE = combined dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide.

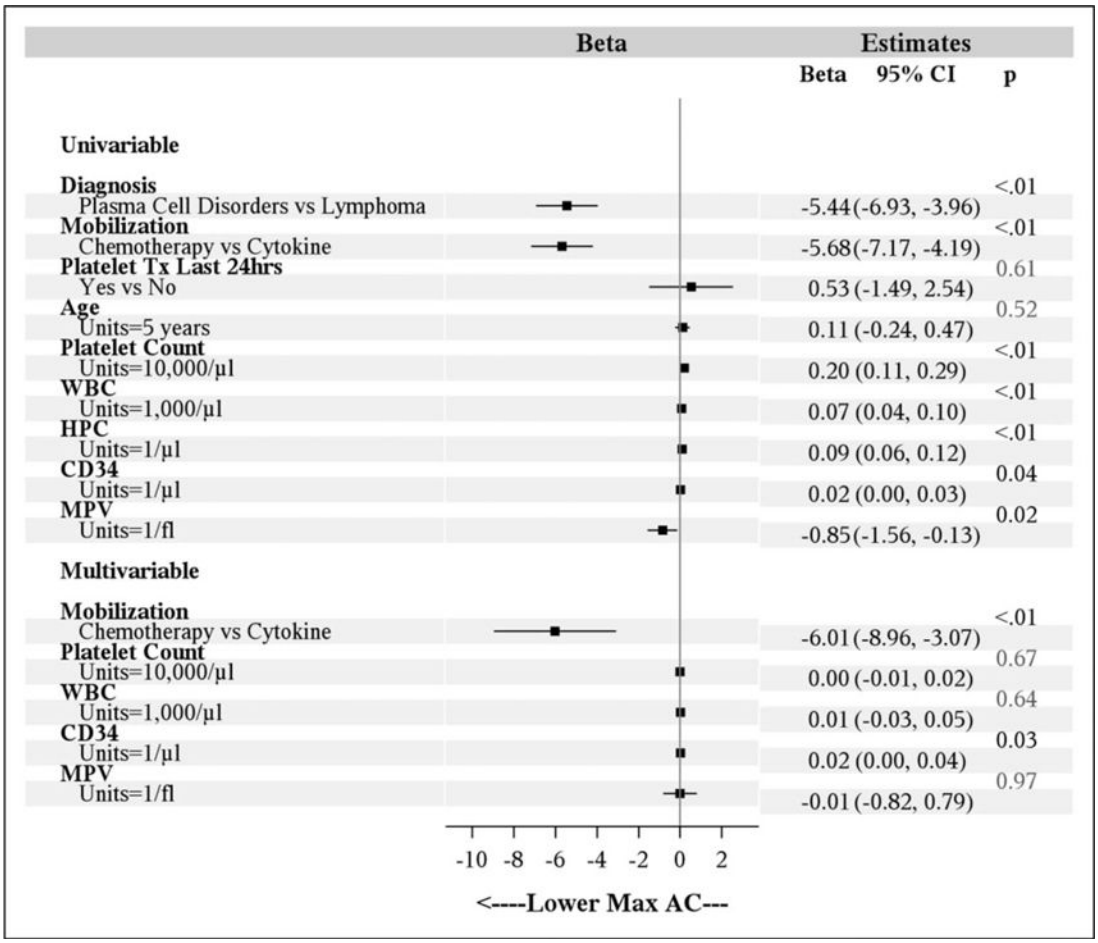

Fig. 4.

Univariable and multivariable analyses of associations between precollection factors and the degree of platelet clumping in the entire study population. OR = odds ratio; CI = confidence interval; Tx = treatment; WBC = white blood cells; HPC = hematopoietic progenitor cells; MVP = mean platelet volume.

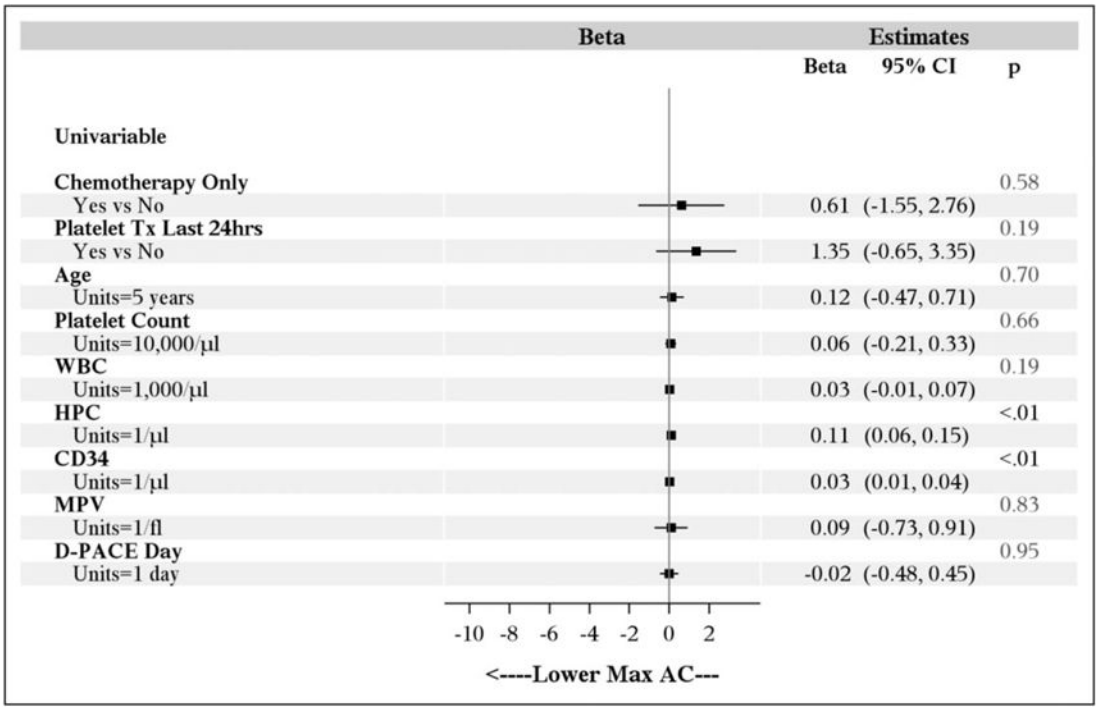

Fig. 5.

Univariable analysis of associations between precollection factors and the degree of platelet clumping in the chemotherapy-mobilized subgroup. C = confidence interval; Tx = treatment; WBC = white blood cells; HPC = hematopoietic progenitor cells; MPV = mean platelet volume; E-PACE = combined dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide.

TABLE 1

Patient characteristics, N = 116

Characteristic	No. of patients
Sex, men:women	70:46
Diagnosis, plasma cell disorders:lymphoma	75:41
Mobilization, chemotherapy:cytokines	68:48
Age: Median (range), y	59 (18–77)

TABLE 2

Patient laboratory values on the day of hematopoietic stem cell collection

Variable	No. of patients	Median (range)
Platelets, 1000/μL	258	68.5 (13–360)
WBCs, 1000/μL	258	27.6 (1.6–128.7)
HPCs/μL	156	10.8 (0.5–60)
CD34+ cells/μL	187	28 (3.4–268.3)

WBCs = white blood cells; HPCs = hematopoietic progenitor cells.

TABLE 3

Characteristics of apheresis and patient parameters at the time of hematopoietic stem cell collection

Variable	All collections	Clumping absent	Clumping present
Apheresis parameters			
TBV processed, mL *	20,195 [7,394–29,146]	21,811 [11,533–29,146]	19,736 [7,394–27,888]
Collection efficiency, % *	64 [12–241]	56 (17–163)	71 (12–241)
Minimum WB:AC ratio *	18:1 [7:1–26:1]	26:1 (10:1–26:1)	16:1 (7:1–24:1)
Maximum WB flow rate *	82 [10–125]	95 (56–125)	80 (10–117)
Patient parameters			
Collection day postchemotherapy *	16 [13–24]	16 (13–21)	15 (13–24)
Citrate reaction present †	63 (24)	20 (21)	43 (27)

* Data are expressed as median [range].

† Data are expressed as numbers (% of group).

TBV = total blood volume; WB = whole blood; AC =anticoagulant.