Predicting Peripheral Blood Stem Cell Harvest Failure Using Circulating CD34 Levels: Developing Target-Based Cut-Points for Early Intervention

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Abstract

Peripheral Blood Stem Cells (PBSC) are usually mobilized using granulocyte colony stimulating factor (G-CSF) with or without chemotherapy. With the emergence of newer mobilizing agents, predicting poor mobilization may allow early intervention and prevent the costs and complications associated with remobilization. We retrospectively evaluated a cohort of 1556 patients seen between January 2000 and December 2008 with Multiple Myeloma (MM) (565; 36%), Non-Hodgkin's Lymphoma (NHL) (562; 36%), Amyloidosis (345; 22%) or Hodgkin's disease (HD) (94; 6%) initially mobilized with single agent G-CSF. Sensitivity-specificity analysis was used to identify ideal peripheral blood CD34 count (PB-CD34) cut-points that predicted successful collection. In patients with plasma-cell disorders a PB-CD34 of 11/uL, 17/uL, 21/uL, and 28/uL by day 4 or 5 were required to collect a target of 2, 4, 8 or 12 million/kg respectively. A CD34 yield <0.8 million cells/kg on first apheresis also predicted for <2 million CD34/kg. For patients with NHL or HD, a PB-CD34 <6/uL and <15/uL on day 4 or 5 predicted failure to achieve a target collection of 2 and 4 million/kg respectively. This study suggests that PB-CD34 thresholds should be based on collection target to allow for early intervention and prevent collection failures.

Keywords

Multiple Myeloma; Lymphoma; Peripheral CD34 count; Stem Cell Mobilization; Plerixafor; Autologous Stem Cell Transplantation

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INTRODUCTION

High-dose therapy (HDT) followed by Autologous Stem Cell Transplantation (ASCT) is an integral component of management of plasma cell disorders such as multiple myeloma (MM) and light chain amyloidosis (AL).[1–5] In fact, MM remains the most common indication for ASCT in North America. ASCT can also provide a potentially curative option for some patients with relapsed Non-Hodgkin's Lymphoma (NHL) and Hodgkin's Disease (HD).[6–9] Peripheral blood stem cells (PBSC) are the preferred graft type for ASCT given the faster engraftment and potential for less contamination of the infused cells with tumor cells compared to bone marrow. Mobilization of PBSC is typically done using growth factor G-CSF alone or in combination with chemotherapy. Peripheral blood CD34 (PB-CD34) counts have been shown to correlate with PB-CD34 apheresis collections and have been utilized to trigger when apheresis should commence. The success of mobilization is influenced by several factors such as prior therapy, mobilization strategy and underlying disease. [10–16] Patients who are failing to mobilize often have G-CSF dose escalation and if unsuccessful, mobilization reattempted with chemotherapy and G-CSF. More recently, plerixafor (AMD3100), a novel mobilizing agent, has been found to enhance G-CSF based collection in patients with NHL and MM, raising the possibility of early intervention in poor mobilizers[17, 18]. While the relationship between circulating CD34 counts and eventual CD34 yield is well known, it is not clear if the PB-CD34 threshold for initiating apheresis should be tailored to the collection goal in order to avoid failed attempts at stem cell collection.

PATIENTS AND METHODS

We identified from our prospectively maintained database, 910 patients with plasma cell disorders who had a first attempt at G-CSF based PBSC mobilization including MM (565; 62%), or AL (345; 38%); and 656 first-time G-CSF based PBSC mobilizers with NHL(562; 86%) or HD (94; 14%) seen between January 2000 to September 2008. Salvage attempts were excluded, as were first attempts using Cyclophosphamide + G-CSF, plerixafor + G-CSF or G-CSF + GM-CSF combinations. All patients had provided written informed consent for use of their medical records. Approval from the Mayo Foundation Institutional Review Board was obtained in accordance with federal regulations and the Declaration of Helsinki.

Stem cells are usually collected using G-CSF priming, with cyclophosphamide and G-CSF typically used for remobilization in patients who failed the initial attempt or in patients with myeloma with high tumor burden. Patients who had chemotherapy primed mobilization are not included in the current analysis. G-CSF was administered subcutaneously (10ug/kg) daily until the completion of stem cell collection with apheresis beginning on the fifth day after starting G-CSF, provided an adequate PB-CD34 count was reached. Our current practice is to obtain a PB-CD34 on day 4 of G-CSF, with days counted from the first day of G-CSF as day 1. If the PB-CD34 count is >= 10/uL, patients will initiate collection the next day (day 5); otherwise it is rechecked on day 5 and apheresis initiated the next day if they reach the threshold. Number of days of apheresis and when to stop collection were based on either achievement of the predetermined PBSC collection goal or at the discretion of the

primary transplant physician in the patients who were not collecting well. Patients who fail to achieve the threshold PB-CD34 count by day 5 typically had their G-CSF increased to 16 mcg/kg twice daily as per current practice.

PBSC collections were performed using either the Caridian BCT COBE Spectra (Caridian BCT, Lakewood CO, USA) or the Fenwal Amicus (Fenwal Inc., Lake Zurich IL, USA). The Fenwal Amicus was the preferred device for PBSC collection during the period examined with the COBE Spectra used for patients sensitive to fluid volume (e.g. amyloid patients), patients with high platelet counts, and when a Fenwal Amicus device was not available. All PBSC collections had an endpoint of five hours processing time. If the patient's pre-procedure peripheral WBC count was $>35\times10^9$/L, the maximum blood flow rate was 65 ml/min. This was done as previous studies had demonstrated an adverse effect of high WBC on CD34+ cell yields.[19]–[21] If the patient's pre-procedure WBC count was $<35\times10^9$/L, maximum blood flow varied according to the apheresis device and are given below. Anticoagulant was ACD-A (Baxter Healthcare Corp., Deerfield, IL, USA), ACD-A and heparin, or a mixture of ACD-A, normal saline, and heparin. If a patient could not receive heparin, the anticoagulant was ACD-A, anticoagulant (AC) ratio was 12:1, and the maximum blood flow rate was determined by the instrument according to patient blood volume, on both instruments.

Several Fenwal Amicus apheresis systems (Version 2.51) were used. If the patient's pre-procedure peripheral WBC count was 35×10^9/L, the cycle volume was 1400 ml, maximum blood flow rate was 90 ml/min, citrate infusion rate (CIR) was 2.50 mg/kg/min, and the anticoagulant (AC) ratio was 13:1. If the patient's pre-procedure peripheral WBC count was $>35\times10^9$/L, the cycle volume was 1000 ml, CIR was 1.25 mg/kg/min and the anticoagulant ratio was 12:1. The plasma flush setting was 8 ml, the MNC and RBC offset settings were 1.5 and 5.0, respectively, for most of the collections. During the period of March, 2005 to September, 2007 (141 patients), variable MNC (0.0–2.3) and RBC (6.0–9.0) offsets were used to maximize CD34+ cell and lymphocyte content of the product while minimizing granulocyte and platelet content during studies performed at our institution.[22]

Several COBE Spectra apheresis instruments (Version 7) were used. The manual technique with a HCT reading of 1% and collect rate of 1 ml/min was used. If the patient's pre-procedure peripheral WBC count was 35×10^9/L, the maximum blood flow rate was 100 ml/min, the AC infusion rate was 1.0 ml/min/liter total blood volume, and the AC ratio was 26:1. If the patient's pre-procedure peripheral WBC count was $>35\times10^9$/L, the maximum blood flow rate was 65ml/min, the AC infusion rate was 1.0 ml/min/liter total blood volume, and the AC ratio was 12:1.

Sensitivity-specificity analysis was used to define the ideal cut-points for PB-CD34 counts to predict for predefined outcomes. In this current analysis we used a CD34 yield of 2 million CD34 cells/kg as the minimum cells dose required to perform a single ASCT and 4 million CD34 cells/kg as the ideal collection required for a single transplant for MM or lymphoma. The Chi-square and Fisher exact tests were used to compare differences between nominal variables and the Mann–Whitney U-test or Kruskal–Wallis test were used for continuous variables.

RESULTS

Plasma cell disorders

A total of 910 patients with MM or amyloidosis underwent first attempt at stem cell mobilization and were included in the current analysis. Of these 860 patients (94.5%) proceeded to at least one attempt at apheresis either having met the threshold criteria for PB-CD34 count or at physician discretion. Patients underwent a median of 3 apheresis sessions (range; 1–12). Among these 532 (62%) had three sessions or less and 774 (90%) had five or less. The median (range) CD34 cells collection (millions/kg) was 7.96 (0.1–29.7) and the median (range) average daily CD34 cell collection (millions/kg) was 2.35 (0.1–29.7).

We first determined the best day-4 PB-CD34 cutoff as a predictor for collecting at least 2 million CD34 cells/kg and it was found to be 9.2/uL. Six hundred seventy three patients (74%) had a PB-CD34 count of 9.2/uL on day 4. Among those with 9.2/uL, only 1.6% failed to collect at least 2 million compared to 27% who had a PB-CD34 <9.2 (P<0.001). The median (range) PB-CD34 count on day 4 among those failing to collect at least 2 million CD34 cells/kg was 4 (0–54) compared to 19.4 (0–357) among those who succeeded (P<0.001) (Figure 1A)

Patients who did not reach the threshold of 10/uL by day 4 had a repeat testing on day 5. 48% of the 257 patients who failed to reach a PB-CD34 of 10/uL by day 4 achieved this threshold by day 5. The best day-4 PB-CD34 cutoff predicting the probability of achieving the threshold by day 5 was 6/uL, with 89% of patients over 6/uL reaching a day-5 PB-CD34 of 10/uL compared to 35% of the remaining; P< 0.001). The best cutoff for PB-CD34 by day 5 for predicting a collection of at least 2 million CD34 cells/kg 11/uL. If the patient reached a PB-CD34 count of 11/uL by day 4 or day 5 (n=740, 82%), the probability of failing to collect the minimum of 2 million CD34 cells/kg was 2% vs. 35% if it was < 11/uL (P<0.001). The median (range) PB-CD34 count on day 4 or day 5 (whichever was higher) among those failing to collect at least 2 million CD34 cells/kg was 6 (0–54) compared to 21 (0–357) among those who succeeded, P < 0.001 (Figure 1B). The actuarial probability of reaching the minimum goal by days of apheresis depending on whether the goal was reached by day 4 (Group 1), or day 5(Group 2), or not reached (Group 3) is shown in Figure 2.

We then determined cutoffs based on ideal targets using only those patients achieving PB-CD34 count >10/uL by day 4 or day 5, since these patients would have started collection without any change in the mobilization technique such as doubling the dose of growth factor. We considered a maximum of 5 collections to achieve the goal as being ideal, taking into account the most commonly used/desired practice of collecting during weekdays. We used stem cell collections of 4 million CD34 cells/kg, 8 million CD34 cells/kg and 12 CD34 cells million/kg as ideal goals for single, two or three transplants respectively as had been our practice during this study period. Among those with a day 4 or day 5 PB-CD34 >10/uL, 87% collected 4 million/kg within 5 collections or less. The best day 4 or day 5 PB-CD34 predicting 4 million/kg yield within 5 collections or less was 17/uL (P<0.001). Similarly, the best day 4 or day 5 PB-CD34 predicting 8 million CD34 cells/kg yield within 5 collections or less was 21/uL and a 12 million CD34 cells/kg yield was 28/uL. Among those with day 4 or 5 PB-CD34 21/uL, 89% collected 8 million/kg compared to 49% among those with PB-

CD34 <21/uL (P<0.001). Similarly, among those with day 4 or 5 PB-CD34 >28/uL, 79% reached 12 million in 5 days compared to 17% among those with PB-CD34 <28/uL (P < 0.001).

Finally, we examined if poor collection on the first day, despite a PB-CD34 > 10 predicts for poor overall yield. Day 1 collection (million/kg) < 0.8 million CD34 cells/kg best predicted failure to reach eventual target of 2 million CD34 cells/kg, with 38% below the cutoff failing to reach the goal compared to 2% for those above the cutoff (P <0.001).

Lymphoma

A total of 656 patients with lymphoma underwent a first attempt at stem cell mobilization and were included for the current analysis. Of these 565 patients (86%) proceeded to at least one attempt at apheresis either having met the threshold criteria for PB-CD34 count or at physician discretion. Patients underwent a median of 3 apheresis sessions (range; 1–8). Among these 394 (70%) had three sessions or less and 533(94%) had five or less. The median (range) CD34 collection (millions/kg) was 4.65 (0.1–26.8) and the median (range) average daily CD34 collection (millions/kg) was 1.47 (0.1–26.8).

As with the previous cohort, we first determined the best day 4 PB-CD34 cut off for being able to collect at least 2 million CD34 cells/kg to be 9/uL. Three hundred eighty three patients (58%) had a PB-CD34 count of 9/uL on day 4. Among those with 9/uL, only 7% failed to collect at least 2 million CD34 cells compared to 55% who had a PB-CD34 count <9 (P < 0.001). The median (range) PB-CD34 count on day 4 among those failing to collect at least 2 million CD34 cells/kg was 4.4 (0–33) compared to 15 (0–140) among those who succeeded, P <0.001 (Figure 3A).

We then examined the proportion of patients achieving the threshold PB-CD34 of 10/uL by day 5 and found that 37% of the 305 patients who failed to reach a PB-CD34 of 10/uL by day 4 did so by day 5. Similar to myeloma/amyloid cohorts, the best cutoff predicting the probability of achieving the target by day 5 was a PB-CD34 of 6/uL on day 4, with 74% of patients with day 4 PB-CD34 6/uL reaching the threshold on day 5 compared to 19% of the rest (P<0.001). The median (range) PB-CD34 count on day 4 or day 5 (whichever is higher) among those failing to collect at least 2 million CD34 cells/kg was 6.3(0–34) compared to 17(0–140) among those who succeeded, P<0.001 (Figure 3B). The actuarial probability of reaching the minimum goal by days of apheresis depending on whether the goal was reached by day 4 (Group 1), or day 5 (Group 2), or not reached (Group 3) is shown in Figure 4.

We then determined cutoffs based on ideal targets (4 million CD34 cells/kg) using only those patients achieving PB-CD34 count >10/uL by day 4 or day 5. Here too we used a maximum of 5 collections to achieve the goal as being ideal, considering the usual practice of collection during weekdays. The best day 4 or day 5 PB-CD34 predicting a 4-million/kg yield in 5 collections was 15/uL. Among those with day 4 or 5 PB-CD34 15/uL, 2% failed to reach 4 million in 5 days compared to 21% among the rest (P < 0.001).

Finally, we examined if poor collection on first day, despite a PB-CD34 > 10 predicts for poor overall yield. Day 1 collection (million/kg) < 1.1 million CD34 cells/kg best predicted

failure to obtain eventual yield of 2 million CD34 cells/kg, with 38% below the cutoff failing to reach the goal compared to 1% for those above the cutoff (P<0.001).

DISCUSSION

Approximately 10–30% of patients of MM or lymphoma fail to collect the minimum number of CD34+ cells (2 million/Kg) to undergo a single cycle of ASCT. [23–26] This collection failure results in increase resource utilization in terms of marked increase in use of growth factors, mobilization reattempts using chemotherapy, hospitalizations, need for transfusions, and antibiotics for neutropenic fever. While the use of chemotherapy allows better stem cell collection, it lengthens the collection process, delays the platelet engraftment, is associated with increased risk of febrile neutropenia and other infections complications [26].

One of the recent advances in this field has been the introduction of plerixafor (AMD3100), a CXCR4 inhibitor. Interaction of chemokine Stromal Cell Derived Factor 1 (SDF-1) and CXCR4 receptor is an important component of the mechanism of retention of stem cells in the bone marrow [27, 28]. It has been proposed that plerixafor mobilizes CD34 cells by inhibition of SDF-1/CXCR4 interaction responsible for stem cells homing and retention [29, 30]. Plerixafor administered in combination of G-CSF has been shown in phase I and phase II studies to significantly increase the number of PB-CD34 cells by a median of 5 fold and CD34 cell collection [30, 31]. In a phase II crossover study of patients with MM and lymphoma, plerixafor was well tolerated and administration of plerixafor increased the likelihood of obtaining 5×10^6 CD34 cells/Kg and allowed collection of this cell dose in fewer apheresis days compared with G-CSF alone[31]. Results from a phase III study in patients with Non Hodgkin's Lymphoma demonstrated statistically significant superiority of plerixafor in combination with G-CSF in achieving minimal and optimal collections compared to placebo and G-CSF[18]. However routine use of the drug for stem cell collection is limited by the high cost, and the exact patient population where a pharmaco-economic benefit can be obtained by its routine use has not been defined.

Another approach would be to use the drug selectively in patients with high likelihood of collection failure or need for prolonged collection with multiple apheresis sessions. However, predicting likelihood of failure based on PB-CD34 counts or initial collections have not been well studied and in particular among patients planning to collect for more than one transplant. Here, we retrospectively studied a large cohort of patients with MM and lymphoma from our transplant database to define parameters for early identification of patients likely to fail mobilization and hence candidates for early intervention. First of all our study supports the cut point of PB-CD34 10/uL to begin mobilization, the guidelines which we follow currently in our clinical practice. Among the myeloma/amyloidosis cohort, 72% reached the traditional cutoff of 10/uL on day 4, of whom only 1.7% failed to collect at least 2 million CD34 cells/Kg compared to 25% among the rest. Nearly half of the patients who failed to reach a PB-CD34 of 10/uL by day 4 did achieve the number by day 5, and a significant proportion of these patients reached the minimum goal. Taken together, an ability to achieve the threshold of 10/uL at least by day 5 translated to a 97% probability of collecting the minimum number of required cells. However, 40% of those who had counts

<10/uL eventually failed to collect the minimum, despite the standard practice of increasing the growth factor dose highlighting the need for alternate approaches. It appears reasonable to use the day 4 or day 5 PB-CD34 count, since a substantial proportion of patients will achieve the threshold value by day 5 and have similar outcome as those reaching the threshold by day 4. But these patients do collect slower than the patients who reached the threshold on the first day of testing, possibly adding extra days of collection. This once again highlights the need for careful pharmaco-economic analyses before routine adoption of treatment algorithms using plerixafor. While intervention based on these parameters may prevent failure to collect the minimum numbers of cells most would prefer to have 4–5 million CD34 cells/kg cells to reduce the risk of slow or incomplete engraftment. The existing data does not allow for exploration of numbers beyond what had been targeted in routine clinical practice for all patients. However we have been able to show that higher threshold numbers of PB-CD34 cells have to be targeted to achieve the increased goals within an ideal number of apheresis procedures. Other studies have explored alternative approaches to enhancing the stem cell collection yield. Cottler-Fox and colleagues developed a formula that will allow determination of the blood volume to be processed during apheresis based on the number of CD34 cells desired, the PB-CD34 counts, machine collection efficiency and patient weight.[32] This represents another variable that can be modified based on the PB-CD34 counts and thus allowing for efficient stem cell collection process.

In conclusion, this study provides valuable information to guide development of clinically relevant algorithms for cost effective use of newly available drugs like plerixafor. Given that the majority of patients reach the threshold of 10/uL by day 5 and the high rate of success among patients achieving this threshold, we recommend consideration of plerixafor for patients who fail to reach a PB-CD34 count of 6/uL by day 4 or 10/uL by day 5 after starting GCSF. When collection for more than one transplant is planned a higher cutoff commensurate with the intended collection should be used as a trigger for addition of plerixafor. Finally, we recommend initiation of plerixafor in patients who achieve the threshold for PB-CD34 count, but fail to collect at least 1 million CD34 cells/kg on the first day of collection. Given our current observations, we have already implemented algorithms that are being validated.[33] The data confirms the use of current guidelines for PB-CD34 cells counts for initiating apheresis, thus minimizing the risk of complete failure. However, the study highlights the need to use higher PB-CD34 thresholds that are adapted to the targeted collection goal for the particular clinical situation. Finally, identification of poor collectors after the start of collection potentially provides another time point for early intervention, and this needs to be prospectively studied.

Acknowledgments

References

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple

myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996; 335(2):91–7. [PubMed: 8649495]

2. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol. 2006; 24(6):929–36. [PubMed: 16432076]

3. Blade J, Rosinol L, Sureda A, Ribera JM, Diaz-Mediavilla J, Garcia-Larana J, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood. 2005; 106(12):3755–9. [PubMed: 16105975]

4. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003; 348(19):1875–83. [PubMed: 12736280]

5. Fermand JP, Katsahian S, Divine M, Leblond V, Dreyfus F, Macro M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol. 2005; 23(36):9227–33. [PubMed: 16275936]

6. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995; 333(23):1540–5. [PubMed: 7477169]

7. Shipp MA, Abeloff MD, Antman KH, Carroll G, Hagenbeek A, Loeffler M, et al. International Consensus Conference on High-Dose Therapy with Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas: report of the jury. J Clin Oncol. 1999; 17(1):423–9. [PubMed: 10458261]

8. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002; 359(9323):2065–71. [PubMed: 12086759]

9. Gratwohl A, Baldomero H, Frauendorfer K, Urbano-Ispizua A. EBMT activity survey 2004 and changes in disease indication over the past 15 years. Bone Marrow Transplant. 2006; 37(12):1069–85. [PubMed: 16757972]

10. de la Rubia J, Blade J, Lahuerta JJ, Ribera JM, Martinez R, Alegre A, et al. Effect of chemotherapy with alkylating agents on the yield of CD34+ cells in patients with multiple myeloma. Results of the Spanish Myeloma Group (GEM) Study. Haematologica. 2006; 91(5):621–7. [PubMed: 16627253]

11. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Gastineau DA, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. Leukemia. 2007; 21(9):2035–42. [PubMed: 17581613]

12. Mark T, Stern J, Furst JR, Jayabalan D, Zafar F, LaRow A, et al. Stem cell mobilization with cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in multiple myeloma. Biol Blood Marrow Transplant. 2008; 14(7):795–8. [PubMed: 18541199]

13. Mazumder A, Kaufman J, Niesvizky R, Lonial S, Vesole D, Jagannath S. Effect of lenalidomide therapy on mobilization of peripheral blood stem cells in previously untreated multiple myeloma patients. Leukemia. 2008; 22(6):1280–1. author reply 1281–2. [PubMed: 18033320]

14. Paripati H, Stewart AK, Cabou S, Dueck A, Zepeda VJ, Pirooz N, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. Leukemia. 2008; 22(6): 1282–4. [PubMed: 18216870]

15. Perea G, Sureda A, Martino R, Altes A, Martinez C, Cabezudo E, et al. Predictive factors for a successful mobilization of peripheral blood CD34+ cells in multiple myeloma. Ann Hematol. 2001; 80(10):592–7. [PubMed: 11732870]

16. Tricot G, Jagannath S, Vesole D, Nelson J, Tindle S, Miller L, et al. Peripheral blood stem cell transplants for multiple myeloma: identification of favorable variables for rapid engraftment in 225 patients. Blood. 1995; 85(2):588–96. [PubMed: 7529066]

17. DiPersio JF, Stadtmauer EA, Nademanee A, Micallef IN, Stiff PJ, Kaufman JL, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood. 2009; 113(23):5720–6. [PubMed: 19363221]

18. DiPersio JF, Micallef IN, Stiff PJ, Bolwell BJ, Maziarz RT, Jacobsen E, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. J Clin Oncol. 2009; 27 (28):4767–73. [PubMed: 19720922]

19. Burgstaler E, Pineda A, Winters JL. Effects of high whole blood flow rates and high peripheral white blood cell counts on CD34+ yield and cross-cellular contamination. Cytotherapy. 2003; 5:446.

20. Burgstaler E, Pineda A. The negative effect of high peripheral white blood cell count on CD34+ cell recovery. J Clin Apher. 2002; 17(3):148.

21. Cooling L, Hoffmann S, Herrst M, Muck C, Armelagos H, Davenport R. A prospective randomized trial of two popular mononuclear cell collection sets for autologous peripheral blood stem cell collection in multiple myeloma. Transfusion. 2010; 50(1):100–19. [PubMed: 19719472]

22. Burgstaler E, Porrata LF, Markovic SN, Winters JL. Use of various offset settings in the Fenwal Amicus during hematopoietic progenitor cell collection to increase lymphocyte yield and reduce cross-cellular contamination. J Clin Apher. 2010; 25 Epub Ahead of print.

23. Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol Blood Marrow Transplant. 2008; 14(9):1045–56. [PubMed: 18721768]

24. Gordan LN, Sugrue MW, Lynch JW, Williams KD, Khan SA, Wingard JR, et al. Poor mobilization of peripheral blood stem cells is a risk factor for worse outcome in lymphoma patients undergoing autologous stem cell transplantation. Leuk Lymphoma. 2003; 44(5):815–20. [PubMed: 12802919]

25. Kuittinen T, Nousiainen T, Halonen P, Mahlamaki E, Jantunen E. Prediction of mobilisation failure in patients with non-Hodgkin's lymphoma. Bone Marrow Transplant. 2004; 33(9):907–12. [PubMed: 15034543]

26. Gertz MA, Kumar SK, Lacy MQ, Dispenzieri A, Hayman SR, Buadi FK, et al. Comparison of high-dose CY and growth factor with growth factor alone for mobilization of stem cells for transplantation in patients with multiple myeloma. Bone Marrow Transplant. 2009; 43(8):619–25. [PubMed: 18997825]

27. Aiuti A, Webb IJ, Bleul C, Springer T, Gutierrez-Ramos JC. The chemokine SDF-1 is a chemoattractant for human CD34+ hematopoietic progenitor cells and provides a new mechanism to explain the mobilization of CD34+ progenitors to peripheral blood. J Exp Med. 1997; 185(1): 111–20. [PubMed: 8996247]

28. Lapidot T. Mechanism of human stem cell migration and repopulation of NOD/SCID and B2mnull NOD/SCID mice. The role of SDF-1/CXCR4 interactions. Ann N Y Acad Sci. 2001; 938:83–95. [PubMed: 11458529]

29. Liles WC, Broxmeyer HE, Rodger E, Wood B, Hubel K, Cooper S, et al. Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist. Blood. 2003; 102(8):2728–30. [PubMed: 12855591]

30. Liles WC, Rodger E, Broxmeyer HE, Dehner C, Badel K, Calandra G, et al. Augmented mobilization and collection of CD34+ hematopoietic cells from normal human volunteers stimulated with granulocyte-colony-stimulating factor by single-dose administration of AMD3100, a CXCR4 antagonist. Transfusion. 2005; 45(3):295–300. [PubMed: 15752146]

31. Flomenberg N, Devine SM, Dipersio JF, Liesveld JL, McCarty JM, Rowley SD, et al. The use of AMD3100 plus G-CSF for autologous hematopoietic progenitor cell mobilization is superior to G-CSF alone. Blood. 2005; 106(5):1867–74. [PubMed: 15890685]

32. Cottler-Fox MH, Lapidot T, Petit I, Kollet O, DiPersio JF, Link D, et al. Stem cell mobilization. Hematology Am Soc Hematol Educ Program. 2003:419–37. [PubMed: 14633793]

33. Micallef I, Ansell SM, Buadi F, Dingli D, Dispenzieri A, Gastineau D, et al. A Risk Adapted Approach Utilizing Plerixafor in Autologous Peripheral Blood Stem Cell Mobilization. ASH Annual Meeting Abstracts. 2009; 114(22):3211.
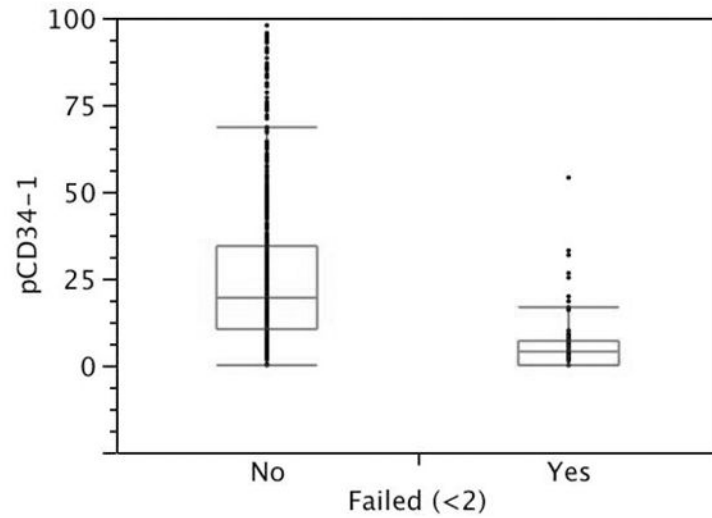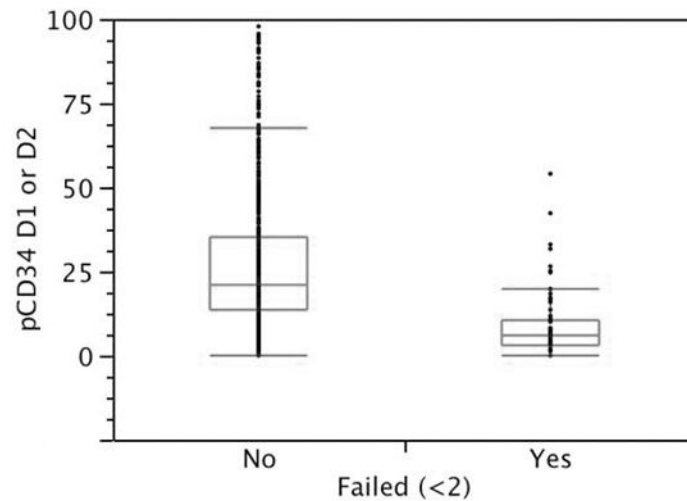
Figure 1A

Figure 1B

Figure 1.
Represents the analysis in patients with Plasma Cell Disorders. ***Panel 1A***: The median
(range) pCD34 count on day 4 among those failing to collect at least 2 million CD34+
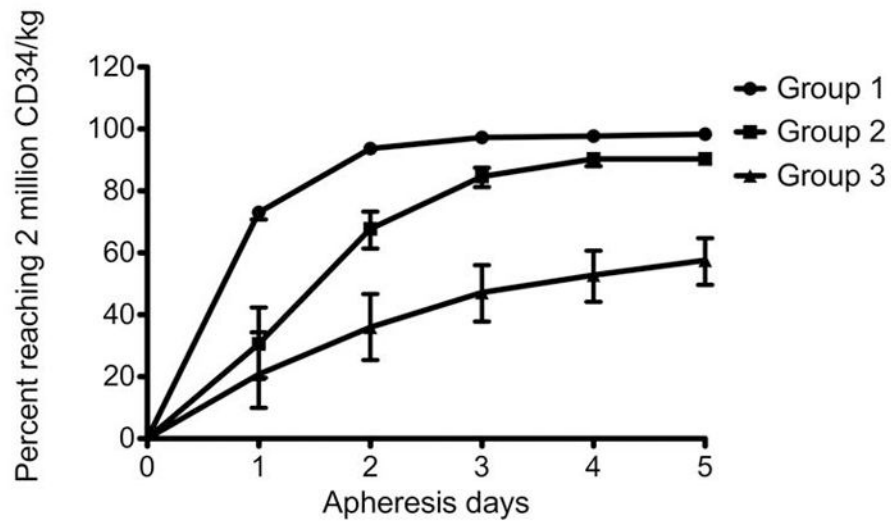cells/kg was 4 (0–54) compared to 19.4 (0–357) among those who succeeded (P<0.001) in
patients with Multiple Myeloma. ***Panel 1B***: The median (range) pCD34 count on day 4 or
day 5 (whichever is higher) among those failing to collect at least 2 million CD34+ cells/kg
was 6 (0–54) compared to 21 (0–357) among those who succeeded, (P < 0.001).

Figure 2.
The graph showing the actuarial probability of reaching the minimum goal (2 million
CD34+ cells/Kg) by days of apheresis depending on the whether the target threshold
(10/uL) was reached by day 4(Group 1), or day 5 (Group 2), or not (Group 3),(P<0.001) in
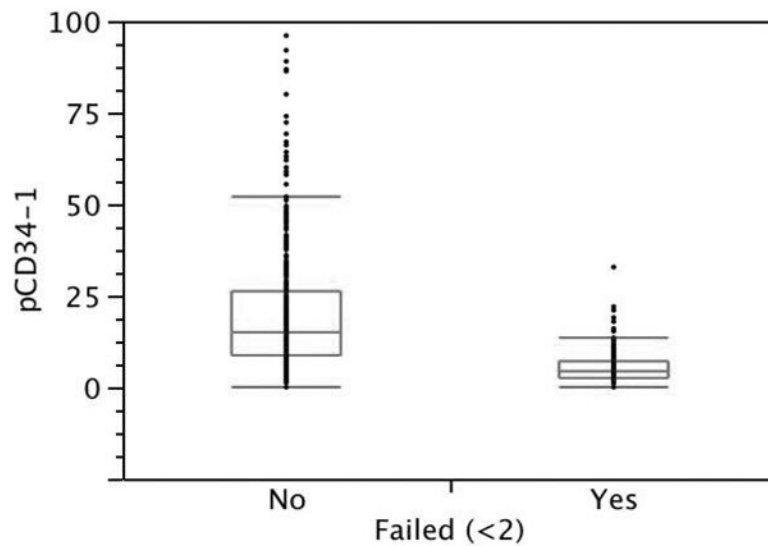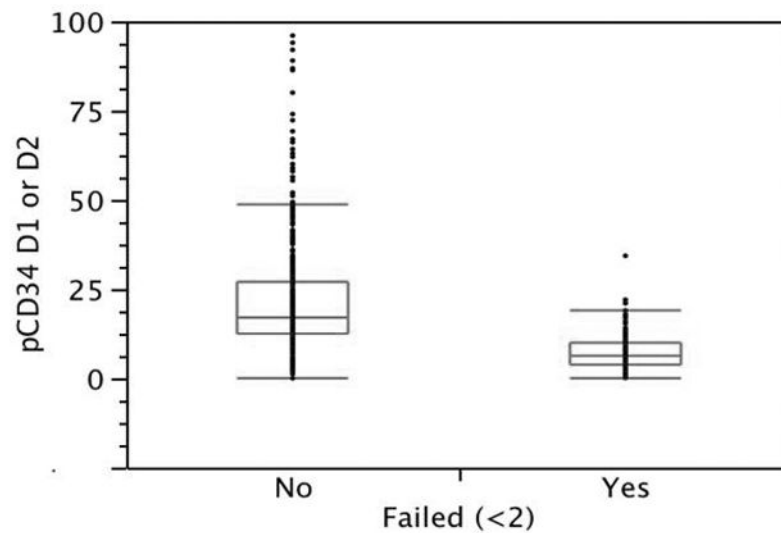patients with Plasma Cell Disorders.

Figure 3A

Figure 3B

Figure 3.
Represents the results obtained in patients with lymphoma. *Panel 3A*: Shows the median (range) pCD34 count on day 4 among those failing to collect at least 2 million CD34+ cells/kg was 4.4 (0–33) compared to 15 (0–140) among those who succeeded, (P <0.001). *Panel 3B*: The median (range) pCD34 count on day 4 or day 5 (whichever is higher) among those failing to collect at least 2 million CD34+ cells/kg was 6.3 (0–34) compared to 17 (0–140) among those who succeeded, (P <0.001).
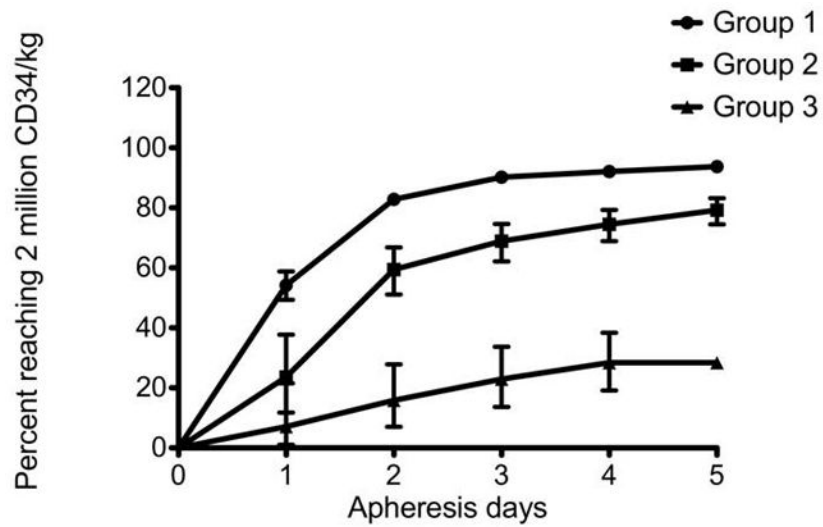
Figure 4.
The figure shows the actuarial probability of reaching the 2 million CD34+ cells/Kg by days of apheresis depending on the whether the goal (10/uL) was reached by day 4 (Group 1), or day 5 (Group 2), or not reached (Group 3), (P<0.001) in patients with lymphoma.