A single center’s experience using four different front line mobilization strategies in lymphoma patients planned to undergo autologous hematopoietic cell transplantation

Bradley M. Haverkos, MD, MPH1, Ying Huang, MS2, Patrick Elder, MS2, Lynn O’Donnell, PhD2, Diane Scholl, RN2, Becky Whittaker, RN2, Sumi Vasu, MBBS2, Sam Penza, MD2, Leslie A. Andritsos, MD2, Steven M. Devine, MD2, and Samantha M. Jaglowski, MD, MPH2
1University of Colorado, Aurora, CO
2The Ohio State University, Columbus, OH

Abstract

In an otherwise eligible patient with relapsed lymphoma, inadequate mobilization of peripheral blood stem cells is a limiting factor to proceeding with an autologous hematopoietic cell transplantation (auto-HCT). Multiple strategies have been used to mobilize an adequate number of hematopoietic stem cells (HSCs) with no obvious front-line strategy. We report a single institutional experience mobilizing HSCs using four different approaches in lymphoma patients. We prospectively collected mobilization outcomes on patients planning to undergo auto-HCT at Ohio State University. We report results of first mobilization attempt for all relapsed or refractory lymphoma patients between 2008–2014. We identified 255 lymphoma patients who underwent mobilization for planned auto-HCT. The 255 lymphoma patients underwent the following front line mobilization strategies: 95 (37%) GCSF alone, 38 (15%) chemomobilization (GCSF + chemotherapy), 97 (38%) preemptive day 4 plerixafor, and 25 (10%) rescue day 5 plerixafor. As expected, there were significant differences between cohorts including age, comorbid indices, histology, and amount of prior chemotherapy. After controlling for differences between groups, the odds of collecting 2×10^6/kg HSCs on the first day of collection and 5×10^6/kg HSCs in total was highest in the cohort undergoing chemomobilization. In conclusion, our experience highlights the effectiveness of chemomobilization.

Keywords
plerixafor; chemomobilization; mobilization; stem cell

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use:http://www.nature.com/authors/editorial_policies/license.html#terms

Corresponding Authors: Brad Haverkos MD, MPH, MS, Assistant Professor, University of Colorado, Division of Hematology, 1665 Aurora Ct. Mail Stop F754 Aurora, CO 80045, Phone: 720 848 8698, Fax: 720 848 5171, bradley.haverkos@ucdenver.edu, Samantha M. Jaglowski, Assistant Professor of Internal Medicine, 320 W. 10th Ave, A352 Starling Loving Hall, Columbus, OH 43210, (614) 293-3196, Fax: (614) 293-7484, Samantha.jaglowski@osumc.edu.

Conflict of Interest: None of the authors have a relevant conflict of interest to report.

Supplementary information is available at Bone Marrow Transplantation’s website.
INTRODUCTION

Autologous hematopoietic cell transplantation (auto-HCT) is a potentially curative therapy for patients with relapsed lymphoma; however, up to 40% of lymphoma patients fail to mobilize adequate numbers of hematopoietic stem cells (HSCs), and thus cannot undergo a therapy known to improve long term survival. Mobilization strategies to achieve adequate apheresis yield for engraftment include cytokine growth factors with or without chemotherapy and the partial CXC chemokine receptor-4 (CXCR-4) antagonist, plerixafor.  

The collection of peripheral blood HSCs is achieved by ≥1 daily leukapheresis sessions, with a goal of minimizing the number of sessions and maximizing total HSC collection. For auto-HCT, a minimum of 2 million CD34+ cells per kilogram (kg) is accepted as sufficient. Transplantation of more than 5 million CD34+ cells per kg is associated with faster hematopoietic recovery, resulting in lower blood transfusions and shorter hospital stay. Two randomized controlled (Phase III) trials in patients with multiple myeloma and non-Hodgkin lymphoma (NHL) showed that addition of plerixafor to granulocyte-colony stimulating factor (GCSF) led to significantly higher peripheral blood CD34+ cells during first mobilization. Since the FDA approval of plerixafor, many institutions administer preemptive plerixafor to individuals with clinical characteristics suggesting a high risk of mobilization failure and as a rescue agent to those failing to mobilize an adequate number of peripheral blood HSCs. Studies evaluating these institutional algorithms typically include both lymphoma and myeloma patients. However, lymphoma patients fail to mobilize adequate HSCs more often than myeloma patients. Furthermore, lymphoma patients frequently receive an intensive chemotherapy regimen to treat the underlying disease prior to auto-HCT, which provides adequate HSC mobilization kinetics when combined with GCSF. There are no prospective comparative analyses between chemomobilization, GCSF alone, GCSF + preemptive plerixafor, and GCSF + rescue plerixafor. Thus, we analyzed our institution’s prospectively collected mobilization outcomes.

METHODS

With IRB approval and patient consent we began prospectively collecting data on patients planned to undergo peripheral blood HSC mobilization for auto-HCT in 2008. In this analysis, we included all relapsed/refractory (R/R) lymphoma patients who underwent their first mobilization attempt between 2008 and 2014 at Ohio State University. We compared mobilization strategies only in the R/R setting; therefore, patients who underwent mobilization after their first chemotherapy regimen were excluded. Only the first mobilization attempt in the R/R setting was studied, thus, mobilization outcomes for subsequent mobilization attempts were excluded from this analysis. From 2008 to 2010, before plerixafor was widely available, our standard mobilization approach was chemomobilization (CM) or cytokine mobilization with GCSF alone. CM was used for patients at high risk of failing to mobilize an adequate amount of stem cells for
auto-HCT. These suspected poor mobilizers underwent CM with cyclophosphamide 3 gm/m² (Cy), etoposide 2000 mg/m², or standard salvage chemotherapy (e.g. ICE, DHAP, ESHAP) at the discretion of the treating physician. In patients undergoing CM, GCSF 10 µg/kg was started on day 5 after chemotherapy. Patients undergoing standard cytokine mobilization without CM also received 10 µg/kg GCSF daily.

Since 2010, our institutional standard is to add plerixafor on the evening of day 4 of GCSF (G+d4 P) for patients who received radiation, ≥10 cycles of chemotherapy, or ≥ age 60. Patients with a CD34+ count of <10/µL on the morning of day 5 of GCSF are given plerixafor later that same evening (G+d5 P). In both approaches, plerixafor 0.24 mg/kg is administered the evening prior to planned apheresis in combination with daily 10 µg/kg GCSF. GCSF + plerixafor is given daily (up to 4 doses of P) until the peripheral blood CD34+ count is ≥10/µL, apheresis is performed using a Caridian Cobe Spectra machine and 4 blood volumes are processed according to institutional guidelines. The target optimal CD34+ cell yield at our institution is >5×10⁶/kg recipient body weight, whereas a minimum dose of at least 2×10⁶/kg is recommended to proceed with auto-HCT.

Baseline characteristics and outcomes were summarized descriptively and compared between different mobilization strategy cohorts using Chi-squared test or the Kruskal-Wallis test for categorical and continuous variables, respectively. Logistic regression models were used to evaluate the effect of clinical factors on the ability to achieve certain collection goals. Poisson regression models were fit using GEE estimation method to assess the association between clinical characteristics and the number of apheresis sessions. Univariable models were first fit for each endpoint. Multivariable models were then constructed using backward elimination where variables were removed based on statistical significance (p>0.05). All multivariable models included mobilization strategy, regardless of statistical significance. Other variable considered included sex, race, Karnofsky performance status (KPS), histology, age, comorbidity index (CMI), number of prior therapies, and radiation. All tests were two-sided, and statistical significance was set at α=0.05.

**RESULTS**

**Patient characteristics**

We identified 255 R/R lymphoma patients who underwent their first mobilization at Ohio State University between 2008 and 2014. Baseline patient characteristics are displayed in table 1. The median age at time of mobilization was 54 (range 19 to 77). The majority of individuals were male (58%) and Caucasian (91%). Histologies were as follows: 95 (37%) classical Hodgkin lymphoma (cHL), 18 (7%) mantle cell lymphoma (MCL), 105 (41%) diffuse large B-cell lymphoma (DLBCL) and 37 (15%) other. The median CMI was 2 (range 0 to 9). Mobilization attempts for 255 R/R lymphoma patients were as follows: 95 (37%) GCSF alone, 38 (15%) CM, 97 (38%) G+d4 P, and 25 (10%) G+d5 P. Three of 38 CM patients received plerixafor. The median first day of collection for the CM cohort was 14 (range 11–26).

The G+d4 P cohort was the oldest (median 62; p<0.0001). The G+d4 P and G+d5 P cohorts had higher proportions of patients with lower KPS (p=0.01) and higher CMI compared to
other cohorts (median 3 vs. 2; p=0.01). There were significant differences in mobilization strategy based on histology (p<0.0001). The majority of patients receiving GCSF alone had cHL (N=64; 67%). Patients receiving CM were distributed similarly across subtypes. The majority of patients receiving G+d4 P had DLBCL (N=66; 68%), whereas a majority of the G+d5 P cohort had cHL (N=13; 52%). The CM and G+d4 P cohorts received the most cycles of prior chemotherapy (median 10; p=0.004). Patients undergoing CM received less radiation but the difference was not significant (p=0.57).

**Mobilization Outcomes**

Of 255 patients undergoing first mobilization, 17 (7%) had inadequate peripheral blood HSC mobilization defined by peripheral blood CD34+ count <10/µL and did not undergo apheresis. Of the remaining 238 patients with adequate peripheral blood CD34+ count, 43 (18%) were unable to achieve a collection total ≥2×10^6 CD34+ cells/kg within 2 days of apheresis. 19 of 43 patients were unable to achieve a total ≥2×10^6 CD34+ cells/kg with additional apheresis days. Table 2 displays outcomes by day of collection. Peripheral blood CD34+ count on 1st day of apheresis was highest in the CM cohort (median 52, range 6–984) (p=0.0006). Correspondingly, the CM cohort required the fewest number of apheresis sessions and had the highest CD34+ collections. Peripheral blood CD34+ count on 1st day of apheresis and CD34+ collections were lowest in the G+d5 P cohort. Total CD34+ collection was highest in patients undergoing CM (median 7.4, range 1–79) and lowest in the G+d5 P cohort (median 2.8, range 1–7) (p<0.0001).

**Odds of collecting ≥ 2 million CD34+ cells/kg on first day of collection**

In the univariable analysis, none of the baseline characteristics except mobilization strategy significantly influenced the odds of collecting ≥2×10^6 CD34+ cells/kg on day 1 of collection. Compared with patients mobilized with GCSF alone, the odds of collecting ≥2×10^6 CD34+ cells/kg on day 1 was 86% lower in patients mobilized with G+d5 P. G+d4 P and CM did not perform significantly different than GCSF alone. Interestingly in multivariable model, after controlling for mobilization strategy, number of prior chemotherapeutic regimens became significant at 0.05 level and remained in the final model. For patients mobilized using the same strategy, the odds of being able to collect ≥2×10^6 CD34+ cells/kg on the first day of collection decreased by 25% with each unit increase in the number of prior chemotherapeutic regimens (Odds ratio (OR) 0.75, 95% CI: 0.59–0.95; p=0.02). For patients with similar number of prior chemotherapy regimens, those who underwent CM were more than twice as likely to collect ≥2×10^6 CD34+ cells/kg on day 1 compared with those who received GCSF alone (OR 2.55, 95% CI: 1.02–6.37; p=0.05). Patients who received G+d5 P were much less likely to achieve ≥2×10^6 CD34+ cells/kg on the first day of collection compared with GCSF alone (OR 0.13, 95% CI: 0.04–0.43; p=0.0008). There was no significant difference between G+d4 P and GCSF alone (OR 0.86, 95% CI: 0.47–1.56; p=0.61) (supplemental table 1).

**Odds of collecting a total of ≥ 2 and ≥ 5 million CD34+ cells/kg**

In univariable analysis, age and histology were the only factors to significantly influence the odds of collecting ≥2 million CD34+ cells/kg in total. For each 5 year increase in age, the odds of collecting ≥2 million CD34+ cells/kg decreased by 21% (OR 0.79, 95% CI: 0.66–
Compared with cHL patients, the odds of collecting $\geq 2 \times 10^6$ CD34+ cells/kg were 73% lower in DLBCL patients (OR 0.27, 95% CI: 0.01–1.00; p=0.05). Notably, the ability to collect $\geq 2 \times 10^6$ CD34+ cells/kg was not significantly different by strategy. Multivariable logistic regression modeling revealed that the only statistically significant variable affecting collection total was age (supplemental table 2).

In univariable analysis, when evaluating the odds of collecting a total of $\geq 5 \times 10^6$ CD34+ cells/kg, mobilization strategy was the only significant factor. Compared with patients mobilized with GCSF, the odds of being able to collect $\geq 5 \times 10^6$ CD34+ cells/kg was 4.12 times greater in patients undergoing CM (OR 4.12, 95% CI: 1.79–9.46; p=0.0009) and 74% lower in patients mobilized with G+d5 P (OR 0.26, 95% CI: 0.07–0.95; p=0.04). In multivariable modeling, after controlling for mobilization strategy, number of prior chemotherapeutic regimens became significant. For patients mobilized using the same strategy, the odds of being able to collect a total of at least $5 \times 10^6$ CD34+ cells/kg decreased as the number of prior chemotherapeutic regimens increased (OR 0.75, 95% CI: 0.58–0.98; p=0.03). For patients with similar number of prior chemotherapy regimens, patients who underwent CM were nearly six times as likely to collect at least $5 \times 10^6$ CD34+ cells/kg (OR 5.82, 95% CI: 2.33–14.52; p=0.0002)) in total. Patients who received G+d5 P were less likely to achieve a total of at least $5 \times 10^6$ CD34+ cells/kg (OR 0.25, 95% CI: 0.07–0.93; p=0.038)). There was no significant difference between G+d4 P and GCSF alone (OR 0.91, 95% CI: 0.49–1.70; p=0.77) (supplemental table 3).

**Number of apheresis sessions**

Seventeen of 255 patients undergoing first mobilization had inadequate peripheral blood HSC mobilization. Poisson models included only 238 patients who had at least one apheresis collection. Compared with patients mobilized by GCSF alone, CM and G+d4 P patients were expected to have 16% (Rate ratio (RR) 0.84, 95% CI: 0.69–1.02; p=0.09) and 9% (RR 0.91, 95% CI: 0.82–1.02; p=0.12) less apheresis sessions respectively, but the difference was not statistically significant. However, G+d5 P patients were expected to have 17% more apheresis sessions (RR 1.17, 95% CI: 1.0–1.35; p=0.04). Mobilization strategy remained as the only significant factor in the multivariable model (supplemental table 4).

**DISCUSSION**

The purpose of this study was to compare outcomes of four different mobilization strategies. We found that patients who underwent chemomobilization (CM) achieved the highest CD34+ collections in the least amount of apheresis days, whereas the G+d5 P achieved the lowest CD34+ collections and required the most apheresis sessions. There were significant differences between cohorts including age, histology, and amount of chemotherapy prior to mobilization, which was in alignment with our institutional algorithm. Specifically, the G+d4 P cohort and CM cohorts were the oldest and most heavily pretreated.

Randomized clinical trials and a Cochrane meta-analysis show that patients receiving G+P have significantly higher mobilization outcomes in comparison to GCSF alone.\textsuperscript{4, 5, 17} To utilize the benefit of plerixafor, our institutional algorithm is to give individuals with clinical characteristics suggesting a high risk of mobilization failure preemptive day 4 plerixafor. We
and others have defined high risk of mobilization as patients who received radiation, ≥10 cycles of chemotherapy, or ≥ age 60.\textsuperscript{18–20} Using this strategy, we observed similar mobilization outcomes with G+d4 P in comparison to GCSF alone. This was despite the GCSF cohort being younger, more fit, and less heavily pretreated. The observation that our G+d4 P outcomes were similar to GCSF alone suggests that the addition of preemptive plerixafor overcomes these high-risk characteristics.

A previous study inclusive of myeloma and lymphoma patients determined the use of rescue (also known as “just in time”) plerixafor was safe, cost effective, and achieved collection totals ≥2×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg in 97% (58/60) patients. However, 45% (27/60) of patients required >2 apheresis sessions.\textsuperscript{21} In our study, the rescue plerixafor (i.e. G+d5 P) cohort had the lowest mobilization outcomes despite being younger and less treated. While 87% of our patients who received rescue plerixafor achieved collection totals ≥2×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg (median 2.8, range 1–7), 48% of our patients required >2 apheresis sessions. These results demonstrate that our algorithm fails to identify a portion of lymphoma patients who mobilize poorly. Other factors such as the underlying disease\textsuperscript{20, 22}, previous bone marrow involvement\textsuperscript{22, 23}, and specific types of chemotherapy\textsuperscript{24–27} may contribute to inferior mobilization in this population. In an Italian study on 215 myeloma and lymphoma patients, fludarabine and low premobilization platelet count were predictors of poor mobilization.\textsuperscript{28}

In one of the few studies studying HSC mobilization only in lymphoma patients, 388 patients were retrospectively studied and low CD34\textsuperscript{+} count in peripheral blood was the only independent risk factor for mobilization failure.\textsuperscript{29} Our previous work\textsuperscript{30} in combination with this study’s results suggest that lymphoma patients who mobilize poorly may not have all the traditional risk factors.

Published mobilization studies typically include myeloma and lymphoma patients and therefore do not include CM outcomes. Along these lines, published mobilization algorithms, including our own, adopt a uniform approach using G+/−P across all auto-HCT patients. This is likely due to both convenience (4–5 days of GCSF vs. >5 for CM), standardization across all disease types, and only a few comparative analyses with CM. In our study, only CM achieved median total collections greater than our goal of 5×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg and impressively had a median collection of 7.4×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg on the first 2 days of apheresis. CM patients were approximately 5× more likely to collect a total of ≥2×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg after controlling for age and 6× more likely to collect ≥5×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg after controlling for amount of prior chemotherapy in comparison to patients mobilized with GCSF alone. Our results suggest CM is an effective mobilization strategy and may be underutilized in the plerixafor era.

While the cohorts have significant differences in baseline characteristics, these results are hypothesis generating and consistent with previous published reports on efficacy of CM. Wood et al. reported CM outcomes in lymphoma patients using etoposide with a median of 6.23×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg (range 0–28) where 95% of patients (N=151/159) achieved successful mobilization (i.e. >2 ×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg).\textsuperscript{31} Others have reported success with alternate CM strategies\textsuperscript{13, 16}, including a study showing that 87% (N=39/45) of patients collected ≥2×10\textsuperscript{6} CD34\textsuperscript{+} cells/kg using a vinorelbine/GCSF approach.\textsuperscript{14} Our study, as well as Wood and colleagues, reported CM collection totals higher than the phase III study with
GCSF alone (median 1.98; range 0–15) and G+P (median 5.69; range 0–29). Two studies have compared front line CM vs. G+P. The PHANTASTIC trial in the United Kingdom compared G+P (N=98) to a historical CM cohort (N=151) and included both myeloma and lymphoma patients. They showed that 25% (N=37) of CM patients failed to achieve ≥2×10^6 CD34+ cells/kg compared to only 4% (N=4) treated with G+P. Overall, median CD34+ collections were similar in each cohort (5.32 G+P vs. 5.02 CM) though, patients in the CM cohort required more apheresis sessions. These results conflict with our findings, albeit this study included both myeloma and lymphoma patients in the CM cohort was a historical cohort that may have used less efficient apheresis techniques. In a more recent study from Dhakal and colleagues, CM with an ifosfamide, carboplatin, etoposide (ICE) provided higher total CD34+ yield and lower rates of mobilization failure in comparison to plerixafor based approaches (p <0.001). Specifically, CM provided a significantly higher total CD34+ cell yield (median collection 5.35×10^6 cells/kg for CM (N=35) vs. 3.15 ×10^6 cells/kg for routine plerixafor (N=30) and 3.6 ×10^6 cells/kg for rescue or “just in time” plerixafor (N=30). There were no mobilization failures (i.e. unable to collect at least 2×10^6 cells/kg) in the CM group, while 5 patients (16.7%) in the routine plerixafor and 3 patients (9.1%) in rescue plerixafor group had mobilization failure (p=0.04).

Any clinical research is flawed by sampling errors, inaccurate data entry, and subjective interpretation. We acknowledge these flaws, the need for further validation, and heterogeneity among patients as limitations of this study. However, this data was prospectively collected on consecutive patients seen at our institution. Thus, the completeness of the data in addition to the real world data collection without exclusion criteria limits our biases. Regardless of bias and cohort heterogeneity the results provide valuable information for future hypothesis driven studies. These results show that our current preemptive (G+d4 P) fails to identify a small portion of lymphoma patients at significant risk of mobilization failure. Furthermore, our results suggest that CM is an effective mobilization strategy for lymphoma patients, especially in light of our previous work showing that plerixafor can rescue CM patients with low peripheral blood CD34+ counts. In this study only 3 of 38 CM patients received rescue plerixafor. We recognize the limitations of receiving additional chemotherapy solely for the purpose of mobilization including delaying auto-HCT, resource utilization, and toxicity. Thus, CM may be best utilized and reserved for lymphoma patients who are planned to receive intense salvage chemotherapy to treat their underlying disease prior to auto-HCT. This current study in combination with our previous work has led to a revised institutional approach for lymphoma patients (figure 1). Future studies should compare these mobilization strategies in lymphoma patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

BH was supported by the National Cancer Institute within the National Institutes of Health under Award Number T32CA165998 at the time this study was initiated.
REFERENCES

1. Sheppard D, Bredeson C, Allan D, Tay J. Systematic review of randomized controlled trials of hematopoietic stem cell mobilization strategies for autologous transplantation for hematologic malignancies. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2012; 18(8):1191–1203.

2. Devine SM, Flomenberg N, Vesole DH, Liesveld J, Weisdorf D, Badel K, et al. Rapid mobilization of CD34+ cells following administration of the CXCR4 antagonist AMD3100 to patients with multiple myeloma and non-Hodgkin's lymphoma. J Clin Oncol. 2004; 22(6):1095–1102. [PubMed: 15020611]

3. 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):1867–1874. [PubMed: 15890685]

4. 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):4767–4773. [PubMed: 19720922]

5. 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):5720–5726. [PubMed: 19363221]

6. Chabannon C, Bijou F, Miclea JM, Milpied N, Grouin JM, Molty M. A nationwide survey of the use of plerixafor in patients with lymphoid malignancies who mobilize poorly demonstrates the predominant use of the "on-demand" scheme of administration at French autologous hematopoietic stem cell transplant programs. Transfusion. 2015; 55(9):2149–2157. e-pub ahead of print 2015/05/15. [PubMed: 25968564]

7. Sheppard D, Bredeson C, Huebsch L, Allan D, Tay J. A plerixafor-based strategy allows adequate hematopoietic stem cell collection in poor mobilizers: results from the Canadian Special Access Program. Bone marrow transplantation. 2014; 49(6):751–755. e-pub ahead of print 2014/03/13. [PubMed: 24614838]

8. Cheng J, Schmitt M, Wuchter P, Buss EC, Witzens-Harig M, Neben K, et al. Plerixafor is effective given either preemptively or as a rescue strategy in poor stem cell mobilizing patients with multiple myeloma. Transfusion. 2015; 55(2):275–283. e-pub ahead of print 2014/08/15. [PubMed: 25117969]

9. Veeraputhiran M, Jain T, Cronin S, Al-Kadhimi Z, Abidi MH, Ayash L, et al. Successful hematopoietic stem cell collection in patients who fail initial plerixafor mobilization for autologous stem cell transplant. J Clin Apher. 2014; 29(6):293–298. [PubMed: 24700728]

10. Storch E, Mark T, Aveccila S, Pagan C, Rhodes J, Shore T, et al. A novel hematopoietic progenitor cell mobilization and collection algorithm based on preemptive CD34 enumeration. Transfusion. 2015; 55(8):2010–2016. [PubMed: 25808119]

11. Chow E, Rao KV, Wood WA, Covington D, Armistead PM, Coghill J, et al. Effectiveness of an algorithm-based approach to the utilization of plerixafor in patients undergoing chemotherapy-based stem cell mobilization. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2014; 20(7):1064–1068.

12. Bilgin YM, Visser O, Beckers EA, te Boome LC, Huisman C, Ypma PF, et al. Evaluation of Dutch guideline for just-in-time addition of plerixafor to stem cell mobilization in patients who fail with granulocyte-colony-stimulating factor. Transfusion. 2015; 55(5):1021–1027. e-pub ahead of print 2015/02/03. [PubMed: 25641128]

13. Jagasia MH, Savani BN, Neff A, Dixon S, Chen H, Pickard AS. Outcome, toxicity profile and cost analysis of autologous stem cell mobilization. Bone marrow transplantation. 2011; 46(8):1084–1088. e-pub ahead of print 2010/11/03. [PubMed: 21042307]

14. Heizmann M, O'Meara AC, Moosmann PR, Heijnen IA, Zubebuhler M, Fernandez P, et al. Efficient mobilization of PBSC with vinorelbine/G-CSF in patients with malignant lymphoma.
15. Copelan E, Pohlman B, Rybicki L, Kalaycio M, Sobecks R, Andresen S, et al. A randomized trial of etoposide and G-CSF with or without rituximab for PBSC mobilization in B-cell non-Hodgkin's lymphoma. Bone marrow transplantation. 2009; 43(2):101–105. e-pub ahead of print 2008/09/17. [PubMed: 18794865]

16. Mahinda A, Bolwell BJ, Rybicki L, Elder P, Kalaycio M, Dean R, et al. Etoposide plus G-CSF priming compared with G-CSF alone in patients with lymphoma improves mobilization without an increased risk of secondary myelodysplasia and leukemia. Bone marrow transplantation. 2012; 47(2):231–235. e-pub ahead of print 2011/04/05. [PubMed: 21460870]

17. Hartmann T, Hubel K, Monsef I, Engert A, Skoetz N. Additional plerixafor to granulocyte colony-stimulating factors for haematopoietic stem cell mobilisation for autologous transplantation in people with malignant lymphoma or multiple myeloma. The Cochrane database of systematic reviews. 2015; 10:Cd010615. e-pub ahead of print 2015/10/21.

18. To LB, Levesque JP, Herbert KE. How I treat patients who mobilize hematopoietic stem cells poorly. Blood. 2011; 118(17):4530–4540. e-pub ahead of print 2011/08/13. [PubMed: 21832280]

19. Stiff PJ. Management strategies for the hard-to-mobilize patient. Bone marrow transplantation. 1999; 23(Suppl 2):S29–S33. e-pub ahead of print 1999/05/21. [PubMed: 10335874]

20. Hosing C, Saliba RM, Ahlawat S, Korbling M, Kebrica P, Alousi A, et al. Poor hematopoietic stem cell mobilizers: a single institution study of incidence and risk factors in patients with recurrent or relapsed lymphoma. American journal of hematology. 2009; 84(6):335–337. e-pub ahead of print 2009/04/23. [PubMed: 19384931]

21. Veltri L, Cumpston A, Shillingburg A, Wen S, Luo J, Leadmon S, et al. Hematopoietic progenitor cell mobilization with "just-in-time" plerixafor approach is a cost-effective alternative to routine plerixafor use. Cytotherapy. 2015; 17(12):1785–1792. e-pub ahead of print 2015/10/18. [PubMed: 26475754]

22. Micaleff IN, Apostolidis J, Rohatiner AZ, Wiggins C, Crawley CR, Foran JM, et al. Factors which predict unsuccessful mobilisation of peripheral blood progenitor cells following G-CSF alone in patients with non-Hodgkin's lymphoma. The hematology journal : the official journal of the European Haematology Association / EHA. 2000; 11(6):367–373. e-pub ahead of print 2002/03/29.

23. Kuittinen T, Nousiainen T, Halonen P, Mahlamaki E, Jantunen E. Prediction of mobilisation failure in patients with non-Hodgkin's lymphoma. Bone marrow transplantation. 2004; 33(9):907–912. e-pub ahead of print 2004/03/23. [PubMed: 15034543]

24. Clark RE, Brammer CG. Previous treatment predicts the efficiency of blood progenitor cell mobilisation: validation of a chemotherapy scoring system. Bone marrow transplantation. 1998; 22(9):859–863. e-pub ahead of print 1998/11/25. [PubMed: 9827813]

25. Tournilhac O, Cazin B, Lepretre S, Divine M, Maloum K, Delmer A, et al. Impact of frontline fludarabine and cyclophosphamide combined treatment on peripheral blood stem cell mobilization in B-cell chronic lymphocytic leukemia. Blood. 2004; 103(1):363–365. e-pub ahead of print 2003/09/13. [PubMed: 12969985]

26. Hill BT, Rybicki L, Smith S, Dean R, Kalaycio M, Pohlman B, et al. Treatment with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone combined with cytarabine and methotrexate results in poor mobilization of peripheral blood stem cells in patients with mantle cell lymphoma. Leukemia & lymphoma. 2011; 52(6):986–993. e-pub ahead of print 2011/02/15. [PubMed: 21314484]

27. Kumar S, Giralt S, Stadtmauer EA, Harousseau JL, Palumbo A, Bensinger W, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. Blood. 2009; 114(9):1729–1735. e-pub ahead of print 2009/06/30. [PubMed: 19561323]

28. Lanza F, Lemoli RM, Olivieri A, Laszlo D, Martino M, Specchia G, et al. Factors affecting successful mobilization with plerixafor: an Italian prospective survey in 215 patients with multiple myeloma and lymphoma. Transfusion. 2014; 54(2):331–339. e-pub ahead of print 2013/06/21. [PubMed: 23781769]

29. Rossi G, Skert C, Morello E, Almici C, Arcaini L, Basilico C, et al. PBSC mobilization in lymphoma patients: analysis of risk factors for collection failure and development of a predictive model. Blood. 2008; 111(11):5097–5104. e-pub ahead of print 2008/06/24. [PubMed: 18524246]
score based on the kinetics of circulating CD34+ cells and WBC after chemotherapy and G-CSF mobilization. Hematological oncology. 2015; 33(3):125–132. e-pub ahead of print 2014/06/04. [PubMed: 24890497]

30. Haverkos BM, McBride A, O'Donnell L, Scholl D, Whittaker B, Vasu S, et al. An effective mobilization strategy for lymphoma patients after failed upfront mobilization with plerixafor. Bone marrow transplantation. 2014

31. Wood WA, Whitley J, Goyal R, Brown PM, Sharf A, Irons R, et al. Effectiveness of etoposide chemomobilization in lymphoma patients undergoing auto-SCT. Bone marrow transplantation. 2013; 48(6):771–776. e-pub ahead of print 2012/11/21. [PubMed: 23165501]

32. Dhakal B, Veltri LW, Fenske TS, Eastwood D, Craig MD, Cumpston A, et al. Hematopoietic Progenitor Cell Mobilization with ICE Chemotherapy Versus Plerixafor-Based Strategies in Patients with Hodgkin and Non-Hodgkin Lymphoma. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016 e-pub ahead of print 2016/06/28.

33. Clark RE, Bell J, Clark JO, Braithwaite B, Vithanarachchi U, McGinnity N, et al. Plerixafor is superior to conventional chemotherapy for first-line stem cell mobilisation, and is effective even in heavily pretreated patients. Blood cancer journal. 2014; 4:e255. e-pub ahead of print 2014/11/02. [PubMed: 25360901]
Figure 1.
Three different mobilization strategies for relapsed or refractory lymphoma patients. Our data suggests that all three of these mobilization strategies are effective and can be used in lymphoma patients. Additionally, we suggest that chemomobilization is an underutilized, yet very effective strategy. There is no randomized data to guide selection among these three strategies. Poor mobilizers defined as those that previously failed CM mobilization or planned P mobilization for those pts who received radiation, ≥ 10 cycles of chemotherapy, or age ≥ 60; G=GCSF; P=plerixafor; d=day; PB=peripheral blood; ICE=ifosfamide, carboplatin, etoposide; DHAP=dexamethasone, high dose cytarabine, cisplatin; Cy=cyclophosphamide; VP-16=etoposide.
Table 1
Characteristics of R/R Lymphoma Patients according to first mobilization strategy

|                     | All patients (N=255) | GCSF (G) alone (N=95) | Chemomobilization (CM) (N=38) | G+ d4 Plerixafor (N=97) | G + d5 Plerixafor (N=25) | p-value |
|---------------------|----------------------|-----------------------|-------------------------------|-------------------------|--------------------------|---------|
| Age at Treatment, year |                      |                       |                               |                         |                          |         |
| Mean (standard deviation) | 50 (16)              | 42 (14)               | 49 (18)                       | 60 (11)                 | 44 (14)                  | <.0001  |
| Median (range)       | 54 (19–77)           | 39 (19–75)            | 57 (21–74)                    | 62 (19–77)              | 43 (21–64)               |         |
| Gender, N (%)        |                      |                       |                               |                         |                          |         |
| Male                | 148 (58)             | 55 (58)               | 25 (66)                       | 56 (58)                 | 12 (48)                  | 0.58    |
| Female              | 107 (42)             | 40 (42)               | 13 (34)                       | 41 (42)                 | 13 (52)                  |         |
| Race, N (%)          |                      |                       |                               |                         |                          |         |
| Caucasian           | 232 (91)             | 84 (88)               | 34 (89)                       | 91 (94)                 | 23 (92)                  | 0.60    |
| Others              | 23 (9)               | 11 (12)               | 4 (11)                        | 6 (6)                   | 2 (8)                    |         |
| Karnofsky Score (KPS), N (%) |               |                       |                               |                         |                          |         |
| 70/80               | 74 (29)              | 18 (19)               | 11 (29)                       | 37 (38)                 | 8 (32)                   |         |
| 90                  | 136 (53)             | 52 (55)               | 18 (47)                       | 52 (54)                 | 14 (56)                  | 0.01    |
| 100                 | 45 (18)              | 25 (26)               | 9 (24)                        | 8 (8)                   | 3 (12)                   |         |
| Comorbid Index (CMI) |                      |                       |                               |                         |                          |         |
| Mean (standard deviation) | 2.7 (2.0)           | 2.3 (1.7)             | 2.4 (2.0)                     | 3.1 (2.2)               | 3.2 (1.7)                | 0.01    |
| Median (range)       | 2 (0–9)              | 2 (0–8)               | 2 (0–9)                       | 3 (0–9)                 | 3 (0–8)                  |         |
| Histology, N (%)     |                      |                       |                               |                         |                          |         |
| cHL                 | 95 (37)              | 64 (67)               | 13 (34)                       | 5 (5)                   | 13 (52)                  |         |
| NHL (DLBCL)         | 105 (41)             | 20 (21)               | 12 (32)                       | 66 (68)                 | 7 (28)                   | <.0001  |
| NHL (MCL)           | 18 (7)               | 4 (4)                 | 8 (21)                        | 6 (6)                   | 0 (0)                    |         |
| NHL Others          | 37 (15)              | 7 (7)                 | 5 (13)                        | 20 (21)                 | 5 (20)                   |         |
| Number of Cycles of Prior Chemotherapy |               |                       |                               |                         |                          |         |
| Mean (standard deviation) | 9.6 (3.5)           | 8.8 (2.1)             | 9.7 (4.7)                     | 10.6 (3.9)              | 9.1 (2.5)                | 0.004   |
|                          | All patients (N=255) | GCSF (G) alone (N=95) | Chemomobilization (CM) (N=38) | G + d4 Plerixafor (N=97) | G + d5 Plerixafor (N=25) | p-value |
|--------------------------|----------------------|-----------------------|-----------------------------|-------------------------|-------------------------|---------|
| Median (range)           | 9 (3–27)             | 9 (4–14)              | 10 (3–26)                   | 10 (4–27)               | 9 (5–16)                |         |
| Radiation, N (%)         |                      |                       |                             |                         |                         |         |
| Yes                      | 69 (27)              | 29 (31)               | 7 (18)                      | 26 (27)                 | 7 (28)                  | 0.57    |
| No                       | 186 (73)             | 66 (69)               | 31 (82)                     | 71 (73)                 | 18 (72)                 |         |

NHL = non-Hodgkin’s lymphoma, cHL = classical Hodgkin’s lymphoma, DLBCL = diffuse large B-cell lymphoma, MCL = mantle cell lymphoma
### Table 2

Outcomes of first mobilization attempt according to strategy

|                  | GCSF (G) alone (N=95) | Chemomobilization (CM) (N=38) | G+ d4 plerixafor (N=97) | G + d5 plerixafor (N=25) | p-value |
|------------------|------------------------|-------------------------------|-------------------------|---------------------------|---------|
| **PB CD34⁺ Count** prior to 1ˢᵗ day of apheresis |                       |                               |                         |                           |         |
| Mean (SD)        | 44.8 (44.4)            | 140.9 (209.3)                 | 43.8 (31.4)             | 22.3 (14.1)               | 0.0006  |
| Median (range)   | 26 (10–275)            | 52 (6–984)                    | 36 (6–153)              | 18 (10–68)                |         |
| **CD34⁺ collection** on 1ˢᵗ day of apheresis |                       |                               |                         |                           |         |
| Mean (SD)        | 3.3 (2.7)              | 12.5 (17.8)                   | 3 (2.1)                 | 1.5 (1.3)                 | <0.001  |
| Median (range)   | 2.5 (0.5–15.6)         | 4.6 (0.6–78.6)                | 2.4 (0.5–10.3)          | 1 (0.3–5.9)               |         |
| **CD34⁺ collection** on days 1–2 of apheresis |                       |                               |                         |                           |         |
| Mean (SD)        | 4.3 (2.5)              | 13.9 (17.1)                   | 4.1 (2)                 | 2.7 (1.7)                 | <0.001  |
| Median (range)   | 4 (0.9–15.6)           | 7.4 (0.9–78.6)                | 4 (1.1–10.3)            | 1.8 (0.8–7.1)             |         |
| **Day 1+2 CD34⁺ ≥2×10⁶, N (%)** |                       |                               |                         |                           |         |
| Yes              | 72 (85)                | 34 (92)                       | 78 (84)                 | 11 (48)                   | <0.001  |
| No               | 13 (15)                | 3 (8)                         | 15 (16)                 | 12 (52)                   |         |
| Insufficient PB HSCs | 10                      | 1                             | 4                       | 2                         |         |
| **Total # of Apheresis Sessions** |                       |                               |                         |                           |         |
| Mean (SD)        | 1.9 (1)                | 1.8 (1)                       | 1.9 (0.7)               | 2.4 (0.9)                 | 0.02    |
| Median/Range     | 2 (0–4)                | 1 (1–5)                       | 2 (0–4)                 | 2 (0–4)                   |         |
| **Total CD34⁺ Collection** |                       |                               |                         |                           |         |
| Mean (SD)        | 4.7 (2.3)              | 14.2 (16.9)                   | 4.3 (1.9)               | 3.3 (1.5)                 | <0.001  |
| Median (range)   | 4.4 (0.9–15.6)         | 7.4 (0.9–78.6)                | 4.1 (1.1–10.3)          | 2.8 (0.8–7.1)             |         |
| **Total CD34⁺ ≥2×10⁶, N (%)** |                       |                               |                         |                           |         |
| Yes              | 79 (93)                | 36 (97)                       | 84 (90)                 | 20 (87)                   | 0.42    |
| No               | 6 (7)                  | 1 (3)                         | 9 (10)                  | 3 (13)                    |         |
|                      | GCSF (G) alone (N=95) | Chemomobilization (CM) (N=38) | G + d4 plerixafor (N=97) | G + d5 plerixafor (N=25) | p-value |
|----------------------|-----------------------|-------------------------------|--------------------------|--------------------------|---------|
| Insufficient PB HSCs | 10                    | 1                             | 4                        | 2                        |         |

1 Peripheral blood (PB) CD34 count is displayed as ___ per µL;

2 Collections are displayed as ___×10^6 CD34+ cells per kg

3 Peripheral blood hematopoietic stem cell count was too low to begin apheresis, defined by peripheral blood CD34+ count <10/uL.