HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2015 August 18.

Published in final edited form as:

Bone Marrow Transplant. 2013 June ; 48(6): 771–776. doi:10.1038/bmt.2012.216.

Effectiveness of Etoposide Chemomobilization in Lymphoma Patients Undergoing Autologous Stem Cell Transplantation

William A Wood, MD, MPH, **Julia Whitley, BS**, **Ravi Goyal, MS**, **Andrew Sharf, RN**, **Robert Irons, PA**, **Kamakshi V. Rao, PharmD**, **Amber Essenmacher, PA**, **Jonathan S. Serody, MD**, **Jay M. Coghill, MD**, **Paul M. Armistead, MD, PhD**, **Stefanie Sarantopoulos, MD, PhD**, **Don A. Gabriel, MD, PhD**, and **Thomas C. Shea, MD**

Bone Marrow and Stem Cell Transplantation Program, Division of Hematology and Oncology, Lineberger Comprehensive Center Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Paul Brown, PhD

University of California, Merced, Merced, CA

Abstract

The effectiveness of stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) in lymphoma patients is suboptimal. We reviewed our institutional experience using chemomobilization with etoposide (VP-16; 375mg/m^2 on days +1 and +2) and G-CSF (5ug/kg twice daily from day +3 through the final day of collection) in 159 patients with lymphoma. This approach resulted in successful mobilization (> 2 × 10^6 CD34 cells collected) in 94% of patients (83% within 4 apheresis sessions). 57% of patients collected at least 5 × 10^6 cells in ≤ 2 days and were defined as good mobilizers. The regimen was safe with a low rate of rehospitalization. Average costs were $14,923 for good mobilizers and $27,044 for poor mobilizers ($p<0.05$). Using our data, we performed a 'break-even' analysis that demonstrated that adding two doses of Plerixafor to predicted poor mobilizers at the time of first CD34 count would achieve cost neutrality if the frequency of good mobilizers were to increase by 21%, while the frequency of good mobilizers would need to increase by 25% if three doses of Plerixafor were used. We conclude that chemomobilization with etoposide and G-CSF in patients with lymphoma is effective, with future opportunities for cost-neutral improvement using novel agents.

Keywords

Autologous transplantation; Lymphoma; Etoposide; Outcomes

Correspondence and Reprint Requests to: William Wood, MD, MPH, University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Division of Hematology and Oncology; Campus Box 7305, 3rd Floor, Physicians' Office Building, 170 Manning Drive, Chapel Hill, NC 27599-7305. Phone: 919-843-6517. Fax: 919-966-6735. wawood@med.unc.edu.

This study was presented in abstract form at the American Society of Hematology Annual Meeting in 2011.

Disclaimers: None of the authors have any conflicts of interest to disclose.

Introduction

Autologous stem cell transplantation (ASCT) is a potentially curative strategy in the management of patients with Non-Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma HL) who have relapsed disease.[1] The ability to undergo ASCT depends upon the successful mobilization and collection of stem cells.

G-CSF alone mobilization strategies have the advantage of convenience in scheduling apheresis procedures and sparing of significant side-effects. In lymphoma populations, however, many patients mobilize inefficiently with this strategy. In a recent phase III trial, only 47% of NHL patients mobilized with G-CSF alone collected ≥ 2×10^6 CD34 cells.[2] In a retrospective review of 656 lymphoma patients mobilized with G-CSF alone, 14% did not proceed to apheresis and 30% of those who proceeded to apheresis required four or more sessions to achieve a minimum of 2×10^6 CD34 cells/kg.[3]

The addition of chemotherapy to G-CSF improves stem cell yield and mobilization outcomes. In a study of chemomobilization with cyclophosphamide, 68% of lymphoma patients collected ≥ 2×10^6 CD 34 cells with a median of 1 apheresis days.[4] Heizmann and colleagues investigated the use of vinorelbine with G-CSF and found that 96% of patients successfully collected sufficient stem cells for ASCT, with a median yield of 3.6×10^6 CD34 cells.[5] Copelan et al. found that 50/55 patients who received full dose etoposide ($2g/m^2$) and G-CSF with or without rituximab as part of a prospective study collected at least 2×10^6CD34 cells and proceeded to ASCT.[6] A larger, retrospective, multi-institutional analysis showed that in comparison to patients receiving G-CSF alone, patients who received etoposide $2g/m^2$ in addition to G-CSF had a higher CD34 cell yield (9.34×10^6 vs. 3.83×10^6) and a higher rate of adequate collection after 2 days (42% vs 16%).[7] Concerns with chemomobilization include the potential for febrile neutropenia, tMDS/AML, and unpredictable timing of collection.

Mozobil (Plerixafor; Genzyme Corporation, Cambridge, MA) is a small molecule that interferes with the binding of stromal cell-derived factor-1a (SDF-1a) with CXC chemokine receptor 4 (CXCR4). In a large phase III study in NHL, the addition of plerixafor to G-CSF led to significantly more patients collecting > 5×10^6 CD34 cells in ≤4 days than G-CSF alone (59% vs 20%). Recent data demonstrate the feasibility of adding plerixafor to conventional chemomobilization regimens.[8] Multiple studies have identified “poor mobilizers” or “failed mobilizers” who experience increased costs and complications relative to “good mobilizers,”[4,9] even if overall post-transplant outcomes are not necessarily inferior.[10] However, it is not clear if plerixafor and G-CSF should replace chemomobilization altogether, or if plerixafor should be integrated into “just in time” or “salvage” strategies in order to improve mobilization outcomes in a cost-neutral way.[11-14] We have previously reported on our experience with chemomobilization using an intermediate intensity etoposide regimen that has led to effective collection of CD34 cells in patients with multiple myeloma.[15] Here, we report our institutional experience with etoposide-based chemomobilization in lymphoma patients, and we propose a rational way in which plerixafor might be integrated into a chemomobilization strategy for selected patients.

Methods

Patients and Treatment

This analysis included patients between the ages of 19 and 75 who received mobilization with VP-16 and G-CSF prior to ASCT for NHL or HL at our institution between June 2004 and September 2010. The mobilization regimen consisted of placement of a central apheresis catheter followed by outpatient administration of intravenous VP-16 (375 mg/m2) once daily on days +1 and +2. Patients received ondansetron 24mg orally and dexamethasone 20mg orally 30 minutes prior to each VP-16 infusion, as well as prochlorperazine 10mg every 4 hours for nausea or emesis. Each VP-16 infusion was diluted to a concentration of 0.4mg/mL and infused over 4 hours, followed by a 20-mL post-infusion saline flush. G-CSF was administered at a dose of 5 ug/kg twice daily starting on day +3 and continuing through the last day of stem cell collection. Antimicrobial prophylaxis was given concurrently using levofloxacin 500mg orally once daily to all patients starting on day +5. Peripheral blood CD34+ cell counts were checked starting on day +12, except for circumstances in which patients were noted to have white blood counts within the normal range or greater than the upper limit of normal at the time of routine monitoring at a pre D+12 office visit. Apheresis was initiated when the peripheral blood CD34+ cell count was ≥7/uL,[16] and all patients had stem cells collected between days +7 and +13. Target volumes were calculated based on an algorithm that includes the patient's weight in kilograms, the peripheral pre-collection CD34+ count, and the requested cell dose (usually a minimum of 5×10^6 CD34+ cells/kg and a target of 8×10^6 CD34+ cells/kg; however, some patients collecting between 5×10^6 CD34+ cells/kg and 8×10^6 CD34+ cells/kg did not attempt further days of collection, according to physician preference). All collections were done using the COBE Spectra machine (CaridianBCT, Lakewood, CO). Platelet transfusions were administered routinely for platelet counts ≤10,000, with higher thresholds used for patients at a higher risk for clinically significant bleeding.

Efficacy, Safety, and Cost Data

Cell yields, other clinical endpoints, and complication data were abstracted from medical records by chart review. A small number of patients had missing values of baseline platelet and white blood cell (WBC) counts (n=4 and 5, respectively); missing values in platelet and WBC count values were imputed with their respective arithmetic means. Inpatient admissions were tabulated and analyzed using University of North Carolina hospital data and chart review for outside hospitalizations. Data on costs were analyzed for all patients. Individualized costs were identified on a per-patient basis and included all non-drug and drug charges. Non-drug charges included catheter insertion, infusion, laboratory draws, provider visits, apheresis procedures, cryopreservation, blood and platelet transfusions, and inpatient admission charges if necessary. These costs were derived from institutional billing data. For chemotherapeutic agents and supportive medications, average wholesale price (AWP) was determined from the Redbook 2010 edition. AWP was adjusted to average sales price (ASP) using the calculation: ASP = AWP – (AWP × 0.2), reflecting an estimated 20% margin of difference.

Total mobilization related costs were separated by the phase of mobilization and also included unexpected health service utilization. Expected costs included medications (chemotherapy, G-CSF, oral antibiotics), mobilization services (catheter placement, chemotherapy infusion), laboratory testing (complete blood counts, peripheral blood CD34 count), and collection services (collection, cryopreservation and storage). Unexpected health service utilization costs were also identified by detailed chart review of each participating patient, as well as communication with outside facilities if needed to clarify clinical documentation. These unexpected costs included inpatient hospital stays, platelet and red blood cell transfusions, additional laboratory testing, and intravenous antibiotics.

Statistical Methods

Descriptive statistics were performed on baseline data. “Good mobilizers” were defined as those patients who collected ≥5 × 10^6/kg CD34+ cells in ≤2 days of collection, and “poor mobilizers” were defined as everyone else. Average costs associated with chemomobilization were compared between “good” and “poor” mobilizers using Wilcoxon rank-sum tests. Medians (with range) for the patient characteristics and means (with standard deviation) for cost categories are reported. Predictive probabilities of being a good vs. poor mobilizer at the time of the first peripheral CD34 testing were determined using multivariate logistic regression analysis. Clinically relevant covariates were controlled for in the model; these included age at transplant, gender, time since diagnosis, duration of prior chemotherapy, number of prior chemotherapy regimens, baseline WBC and baseline platelet counts. Average costs were then calculated for new groups of predicted good and poor mobilizers. Break-even analyses were performed under several hypothetical scenarios that included the use of plerixafor. Only significant scenarios have been presented in this paper.

All statistical analyses were performed using SAS© v 9.2 (Cary, NC) at an *a priori* significance level of 0.05.

Results

Patients

A total of 159 patients with lymphoma underwent stem cell mobilization and collection with VP-16 and G-CSF between June 2004 and September 2010. 26 patients received rituximab 375mg/m2 on day +1 for reasons related to enrollment on clinical trials or physician preference. Median age of the sample was 52 years, and more than half of patients were male (62 percent). The median age at the time of transplant was 52 years, with a range of 19 to 75 years. Patients had received an average of 7.5 months of prior chemotherapy (range: 2.5-31 months), with 25 patients (16%) having received 1 prior treatment regimen, 89 (56%) having received 2 prior regimens, 31 (19%) having received 3 prior lines of therapy, and 14(9%) having received at least 4 prior regimens in addition to the etoposide mobilization regimen described here.

Efficacy

Ninety-four percent of all patients (150/159, 94%) were able to collect successfully (> 2 × 10^6 CD34+ cells/kg) after 1 mobilization, with 8 patients (5%) requiring a second

mobilization or bone marrow harvest and 1 patient not proceeding to transplant. 83% of patients achieved successful collection within 4 apheresis days. Patients hospitalized elsewhere for neutropenic fevers returned to the transplant center for successful collection. Patients with positive blood cultures received a minimum of 48 hours of antibiotics and must have been afebrile at the time of apheresis. Using our definition of "good mobilizers" (ability to collect at least 5×10^6 cells/kg in 1-2 days), 57% (n=90) of patients were good mobilizers. Median CD34 cells/kg collected for the entire population was 6.2×10^6, though this number was nearly twice as large in the good vs. poor mobilizing group (8.5×10^6 vs 4.4×10^6). The median number of apheresis days in the entire population was 2, though this was substantially smaller among good mobilizers (median 1 day) vs. poor mobilizers (median 4 days). 109 (70%) of all patients and 82 (91%) of all good mobilizing patients were able to initiate apheresis on or before D+12.

Safety

Most patients underwent at least 1 interim blood count assessment at our institution during the course of mobilization, usually around D+8, with the rest having blood counts checked at outside institutions. 50 (31%) of patients required at least one PRBC transfusion (14% of good mobilizers and 54% of poor mobilizers), and 51 (32%) required at least one platelet transfusion (14% of good mobilizers and 55% of poor mobilizers). Over half of the poor mobilizing patient population required PRBC or platelet transfusions. Ten patients (6%) required inpatient admission during the mobilization period, mostly for febrile neutropenia. These included 2 (2%) of good mobilizers and 8 (12%) of poor mobilizers. There was one case of treatment-related myelodysplasia in a patient who received etoposide mobilization and a BEAM autograft for T cell lymphoma. Cases of tMDS were determined by detailed chart review and long-term follow-up data collection by the transplant center. Efficacy and safety data are presented in Table 1.

Costs

For all patients, the average total cost of chemomobilization was $20,184 (SD, $8,485). The average cost of chemotherapy ($2,371) represented 12% of these total costs, whereas other costs related to mobilization, apheresis, product processing and storage were significantly greater ($15,373). Costs varied markedly between poor and good mobilizers, including costs of unexpected health services utilization beyond the apheresis and cytokines (transfusions, admissions and additional antibiotics), which were over three times greater in poor mobilizers ($3,804 vs. $1,396). Overall, total average costs for poor mobilizers were nearly twice as high as for good mobilizers ($27,045 vs $14,924, $p<0.05$). Cost data are presented in Table 2.

Predictive modeling

In order to identify predictors of good and poor mobilizers, we performed a logistic regression analysis including baseline data as well as the first peripheral blood CD34 count (obtained between D+9 and D+15, with 82% of first counts obtained on D+12). In this model, both a lower first peripheral blood CD34 count ($p<0.001$) and a lower pre-chemotherapy platelet count ($p=0.024$) were found to be statistically significantly associated with poor mobilization. For simplification, we ran a third logistic model using the first

peripheral blood CD34 count alone and found that the first peripheral blood CD34 count was the single most important predictor of good vs. poor mobilization (c-statistic of 0.94), and a cutoff point of an absolute CD34 count of 27/μL in the peripheral blood differentiated good from poor mobilizers. Estimates from this multivariate logistic model are presented in Table 3.

Using these data, we performed analyses under five hypothetical scenarios that incorporated the use of plerixafor (Table 4). For each of these scenarios, we assumed an average sales price for plerixafor of $6000/dose, and a median number of either 3 doses of plerixafor (based on the intervention arm in the phase III trial of plerixafor + G-CSF in NHL patients)[2] or 2 doses of plerixafor. We compared all groups to our current average costs of $20,184 per patient. Under these hypothetical scenarios, we found that only when plerixafor was given to predicted poor mobilizers (based on peripheral blood CD34 count) would predicted costs approximate our current costs, and thus become cost-neutral. In general, cost-neutrality is achieved when an intervention results in savings that are equal to the cost of the intervention, and thus does not increase overall costs. We used this concept of cost-neutrality to determine the desired minimum effectiveness of plerixafor by converting enough patients from the poor mobilizing to good mobilizing category to bring down overall resource utilization and offset the costs of plerixafor. If 3 doses of plerixafor were given to predicted poor mobilizers, 62% of these patients would need to become good mobilizers to achieve cost neutrality, whereas 49% of predicted poor mobilizers would need to become good mobilizers if a median of 2 doses of plerixafor were used. Assumptions underlying these models accompany Table 4.

Table 5 displays the relative contribution of each mobilization component to total costs under the hypothetical scenarios in which two or three doses of plerixafor were given to predicted poor mobilizers.

Discussion

The optimal method for mobilizing patients prior to ASCT for lymphoma remains unclear. Success rates using G-CSF alone are suboptimal, with only 20% of patients in the G-CSF alone control arm of a large Phase III study collecting 5×10^6 CD34 cells within 5 days. Plerixafor has been found to improve outcomes relative to G-CSF alone (59% of patients in the plerixafor group vs 20% in the G-CSF group met the primary endpoint in the phase III study) but is costly and still results in a significant percentage of patients with suboptimal CD34+ cell collections. Though chemomobilization is well-established, this technique comes with risks. We therefore sought to investigate the effectiveness of chemomobilization and to identify cost-effective opportunities for improvement in the current era of plerixafor.

Krishnan et al. reported that chemomobilization with high doses of etoposide ($2g/m^2$ in 51/62 patients, and either $1g/m^2$ or $1.5g/m^2$ in 9 other patients) was associated with a 12.3 fold increased risk of developing t-AML with 11q23/21q22 abnormalities.[17] At our institution, we have therefore used lower dose etoposide ($375mg/m^2 \times 2$ days) in addition to G-CSF as part of a chemomobilization strategy prior to ASCT in an attempt to gain the benefits of chemomobilization without an increased risk of t-MDS or AML. We have

previously demonstrated this approach to be highly effective in patients with multiple myeloma; among 152 patients with multiple myeloma mobilized in this fashion, 100% of patients successfully mobilized with 99% collecting at least 5×10^6 CD34 cells/kg in 1-2 days ("good mobilizers").[15] In the current study, we looked at the effectiveness of this regimen among patients with lymphoma, and although our results were promising (94% achieved successful collection), the proportion of "good mobilizers" (57%) was substantially less than in the myeloma study. Further, we demonstrated that poor mobilizers consumed significantly greater resources and incurred substantially higher costs than good mobilizers, consistent with published data.[18]

Though direct comparisons are unwarranted, as ours was not a randomized study and baseline characteristics among the patient populations may have varied, Table 6 suggests that our results are at least comparable, from an efficacy standpoint, to other mobilization strategies. The CD34 stem cell yield with VP-16 chemomobilization (6.4×10^6) appears similar to the yield from the plerixafor arm in the Dipersio study (5.7×10^6) and better than the G-CSF alone arm (1.98×10^6). Likewise, the percentage of patients collecting at least 2×10^6 CD34 cells/kg or 5×10^6 CD34 cells/kg in ≤ 4 apheresis days appeared similar in our study to the published plerixafor data.

Limitations of chemo-mobilization regimens include short and long term safety concerns of incorporating even intermediate dose chemotherapeutic agents into the mobilization regimen. Indeed, 30% of patients in our study required red blood cell transfusions, 30% required platelet transfusions, and 12% required inpatient admission, mostly for neutropenic fevers. However, much of this resource utilization was driven by poor mobilizers, over half of whom needed transfusions and nearly 20% of whom required inpatient hospitalization during the mobilization period. Costs of mobilization in general were also twice as large in poor mobilizers compared to good mobilizers, with a substantial range of costs in the poor mobilizing population (average cost $27044, St. Dev. $8099).

Thus, a logical strategy to improve upon our results would involve intervening in the case of poorly mobilizing patients, particularly given recent data demonstrating efficacy of plerixafor in G-CSF mobilized patients with low preapheresis peripheral blood CD34 counts.[19] Towards this end, we developed a predictive model based primarily on the first peripheral blood CD34 count. Identifying a cutoff point of 27/μL, we found that the first peripheral blood CD34 count predicted good vs poor mobilizers with favorable test characteristics. Further, we constructed a hypothetical scenario in which cost neutrality could theoretically be achieved by adding plerixafor to the mobilization regimens of patients with an initial peripheral blood CD34 count of less than 27.

Our study has several limitations. First, data were obtained by chart review and tus may have missed resource utilization data points that could have affected the subsequent predictive models. Thus, resource utilization data were reviewed by more than one reviewer, including the entire electronic medical record (outpatient and inpatient notes, transfusion labs, administered blood products, and external communication). Second, although 82% of first peripheral blood CD34 counts were obtained on D+12, the date of first peripheral blood CD34 count acquisition was not uniform. Third, there remains a relative paucity of

published data about the expected efficacy of incorporating plerixafor into chemomobilization regimens. Whether 49% of a predicted poor mobilizing population treated with chemomobilization can be reasonably expected to convert to good mobilizers, as was required in our breakeven model, is not clear. Published data suggest encouraging efficacy in this setting so this may be a reasonable hypothesis to test.[20-22] Finally, we did not include the highly variable costs associated with rescue strategies for failed mobilizations, which limited our ability to make total resource and cost comparisons for strategies (such as G-CSF alone) in which failed mobilizations would be expected to comprise a substantial proportion of the patient population.

Though about a third of patients did require transfusion support, and a small number (especially poor mobilizers) required inpatient hospitalization, there were no treatment-related deaths and only one identified case of treatment related MDS, showing that this regimen is safe. Our modeling suggests that an alternative strategy of planned plerixafor and G-CSF for all patients is not likely to be cost effective. Moving forward, we plan to conduct a prospective trial with a further reduction in the etoposide dose, as well as administration of plerixafor to predicted poor mobilizers, to determine if the efficacy and safety of our regimen can be further improved in a cost-neutral way.

Acknowledgements

Work on this study was supported by the Integrated Cancer Information and Surveillance System (ICISS), UNC Lineberger Comprehensive Cancer Center with funding provided by the University Cancer Research Fund. Work was also supported by NIH CTSA KL2RR025746.

REFERENCES

1. Pasquini MC, Wang Z, Horowitz MM, Gale RP. Current use and outcome of hematopoietic stem cell transplantation: Center for International Blood and Marrow Transplant Research (CIBMTR) Summary Slides. 2010 Available at http://www.cibmtr.org. 2010.
2. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27(28):4767–4773. Prepublished on 2009/09/02 as DOI 10.1200/JCO.2008.20.7209. [PubMed: 19720922]
3. Sinha S, Gastineau D, Micallef I, Hogan W, Ansell S, Buadi F, et al. Predicting PBSC harvest failure using circulating CD34 levels: developing target-based cutoff points for early intervention. Bone marrow transplantation. 2011; 46(7):943–949. Prepublished on 2010/10/12 as DOI 10.1038/bmt.2010.236. [PubMed: 20935680]
4. 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. 2010 Prepublished on 2010/11/03 as DOI 10.1038/bmt.2010.254.
5. Heizmann M, O'Meara AC, Moosmann PR, Heijnen IA, Zuberbühler M, Fernandez P, et al. Efficient mobilization of PBSC with vinorelbine/G-CSF in patients with malignant lymphoma. Bone marrow transplantation. 2009; 44(2):75–79. Prepublished on 2009/01/27 as DOI 10.1038/bmt.2008.434. [PubMed: 19169288]
6. 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. Prepublished on 2008/09/17 as DOI 10.1038/bmt.2008.306. [PubMed: 18794865]

7. Mahindra 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. 2011 Prepublished on 2011/04/05 as DOI 10.1038/bmt.2011.73.
8. Dugan MJ, Maziarz RT, Bensinger WI, Nademanee A, Liesveld J, Badel K, et al. Safety and preliminary efficacy of plerixafor (Mozobil) in combination with chemotherapy and G-CSF: an open-label, multicenter, exploratory trial in patients with multiple myeloma and non-Hodgkin's lymphoma undergoing stem cell mobilization. Bone marrow transplantation. 2010; 45(1):39–47. Prepublished on 2009/06/02 as DOI 10.1038/bmt.2009.119. [PubMed: 19483760]
9. Hosing C, Smith V, Rhodes B, Walters K, Thompson R, Qazilbash M, et al. Assessing the charges associated with hematopoietic stem cell mobilization and remobilization in patients with lymphoma and multiple myeloma undergoing autologous hematopoietic peripheral blood stem cell transplantation. Transfusion. 2011; 51(6):1300–1313. Prepublished on 2011/05/18 as DOI 10.1111/j.1537-2995.2011.03176.x. [PubMed: 21575005]
10. Stockerl-Goldstein KE, Reddy SA, Horning SF, Blume KG, Chao NF, Hu WW, et al. Favorable treatment outcome in non-Hodgkin's lymphoma patients with "poor" mobilization of peripheral blood progenitor cells. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2000; 6(5):506–512. Prepublished on 2000/11/04 as DOI.
11. Li J, Hamilton E, Vaughn L, Graiser M, Renfroe H, Lechowicz MJ, et al. Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics. Transfusion. 2011 Prepublished on 2011/04/16 as DOI 10.1111/j.1537-2995.2011.03136.x.
12. Shaughnessy P, Islas-Ohlmayer M, Murphy J, Hougham M, MacPherson J, Winkler K, et al. Cost and clinical analysis of autologous hematopoietic stem cell mobilization with G-CSF and plerixafor compared to G-CSF and cyclophosphamide. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2011; 17(5):729–736. Prepublished on 2010/09/04 as DOI 10.1016/j.bbmt.2010.08.018.
13. Costa LJ, Alexander ET, Hogan KR, Schaub C, Fouts TV, Stuart RK. Development and validation of a decision-making algorithm to guide the use of plerixafor for autologous hematopoietic stem cell mobilization. Bone marrow transplantation. 2011; 46(1):64–69. Prepublished on 2010/04/13 as DOI 10.1038/bmt.2010.78. [PubMed: 20383210]
14. Costa LJ, Miller AN, Alexander ET, Hogan KR, Shabbir M, Schaub C, et al. Growth factor and patient-adapted use of plerixafor is superior to CY and growth factor for autologous hematopoietic stem cells mobilization. Bone marrow transplantation. 2011; 46(4):523–528. Prepublished on 2010/07/14 as DOI 10.1038/bmt.2010.170. [PubMed: 20622909]
15. Wood WA, Whitley J, Moore D, Sharf A, Irons R, Rao K, et al. Chemomobilization with Etoposide is Highly Effective in Patients with Multiple Myeloma and Overcomes the Effects of Age and Prior Therapy. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2011; 17(1):141–146. Prepublished on 2010/07/20 as DOI 10.1016/j.bbmt.2010.06.021.
16. Bandarenko N, Sims LC, Brecher ME. Circulating CD34+ cell counts are predictive of CD34+ peripheral blood progenitor cell yields. Transfusion. 1997; 37(11-12):1218. author reply 1218-1220. Prepublished on 1998/01/14 as DOI. [PubMed: 9426651]
17. Krishnan A, Bhatia S, Slovak ML, Arber DA, Niland JC, Nademanee A, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood. 2000; 95(5):1588–1593. [PubMed: 10688812]
18. Gertz MA, Wolf RC, Micallef IN, Gastineau DA. Clinical impact and resource utilization after stem cell mobilization failure in patients with multiple myeloma and lymphoma. Bone marrow transplantation. 2010; 45(9):1396–1403. Prepublished on 2010/01/12 as DOI 10.1038/bmt.2009.370. [PubMed: 20062089]
19. Nademanee AP, Dipersio JF, Maziarz RT, Stadtmauer EA, Micallef IN, Stiff PJ, et al. Plerixafor plus granulocyte colony-stimulating factor versus placebo plus granulocyte colony-stimulating factor for mobilization of CD34(+) hematopoietic stem cells in patients with multiple myeloma and low peripheral blood CD34(+) cell count: results of a subset analysis of a randomized trial.

Biology of Blood and Marrow Transplantation. Jun 6.2012 [Epub ahead of print] PMID: 22683613.

20. D'Addio A, Curti A, Worel N, Douglas K, Motta MR, Rizzi S, et al. The addition of plerixafor is safe and allows adequate PBSC collection in multiple myeloma and lymphoma patients poor mobilizers after chemotherapy and G-CSF. Bone marrow transplantation. 2011; 46(3):356–363. Prepublished on 2010/06/26 as DOI 10.1038/bmt.2010.128. [PubMed: 20577218]
21. Jantunen E, Kuittinen T, Mahlamaki E, Pyorala M, Mantymaa P, Nousiainen T. Efficacy of pre-emptively used plerixafor in patients mobilizing poorly after chemomobilization: a single centre experience. Eur J Haematol. 2011; 86(4):299–304. Prepublished on 2011/01/05 as DOI 10.1111/j.1600-0609.2010.01573.x. [PubMed: 21198864]
22. Basak GW, Urbanowska E, Boguradzki P, Torosian T, Halaburda K, Wiktor-Jedrzejczak W. Booster of plerixafor can be successfully used in addition to chemotherapy-based regimen to rescue stem cell mobilization failure. Ann Transplant. 2010; 15(4):61–67. Prepublished on 2010/12/25 as DOI. [PubMed: 21183878]

Table 1

Efficacy and Safety of Chemomobilization.

Parameter	All Patients N = 159	Good Mobilizers N = 90(57%)	Poor Mobilizers N = 69(43%)
Median total $CD34^+$ cells × 10^6/kg N (range)	6.2 (0.0-27.6)	8.5 (5.0-27.6)	4.4 (0.0-8.8)
Median number of apheresis days (range)	2 (0-6)	1 (1-2)	4 (0-6)
Median number of days receiving G-CSF (range)	11 (7-29)	10 (7-11)	13 (11-29)
Number of patients initiating apheresis on or before Day 12 (%)	109 (70)	82 (91)	27 (39)
Mean CD34# on first day tested	78 (0-529)	129 (2-529)	11 (0-43)
Number of patients collecting ≥2 × 10^6CD34^+ cells/kg (%)	150 (94)	90 (100)	60 (87)
Number of patients requiring second mobilization or bone marrow harvest (%)	8 (5)	0 (0)	8 (12)
Number of patients requiring admission during mobilization period (%)	10 (6)	2 (2)	8 (12)
Number of patients requiring at least one PRBC transfusion (%)	50 (31)	13 (14)	37 (54)
Number of patients requiring at least one platelet transfusion (%)	51 (32)	13 (14)	38 (55)
Number of patients requiring additional oral antibiotics (%)	19 (12)	7 (8)	12 (17)

Table 2

Costs Associated with Chemomobilization among good and poor mobilizers

Parameter	All Patients N = 159	Good Mobilizers N = 90	Poor Mobilizers N = 69	P-value[#]
Average cost of mobilization / collection, not including VP-16, Mean (SD[*])	$15372.74 (6772.43)	$11158.01 (3037.09)	$20870.22 (6349.82)	<0.0001
Average cost of etoposide, Mean (SD)	$2370.72 (0.0)	$2370.72 (0.0)	$2370.72 (0.0)	1.0000
Average cost of unexpected health service utilization, Mean (SD)	$2440.23 (2802.14)	$1394.88 (1406.79)	$3803.71 (3510.17)	<0.0001
Average total cost, Mean (SD)	$20183.69 (8485.45)	$14923.62 (3637.88)	$27044.65 (8099.04)	<0.0001

[*] SD=Standard Deviation

[#] Based on the Wilcoxon Rank-sum Tests

Table 3

Predictors of Good vs. Poor at First CD34 Count (c = 0.965)

Parameter	Odds ratio (Point Estimate)	95% Confidence Limits	P
First CD34*	1.112	1.070 - 1.176	<.0001
Age at Time of Mobilization	1.012	0.960 - 1.067	0.6616
Gender	1.535	0.459 - 5.134	0.4867
Time Since Diagnosis	0.994	0.969 - 1.020	0.6747
Duration of Prior Chemotherapy	0.849	0.673 - 1.072	0.1688
Number of Prior Chemotherapy Regimens	1.022	0.332 - 3.150	0.9698
Receipt of Rituxan	0.257	0.060 - 1.096	0.0663
WBC at Mobilization	1.329	0.980 - 1.802	0.0670
*Platelet Count at Mobilization**	1.007	1.001 - 1.013	0.0249

* indicates significant variable at $p<0.05$

Table 4

Cost analyses with the Following Assumptions: N=159 patients; ASP Plerixafor = $6,000/dose

Scenario	# (%) patients receiving plerixafor	Efficacy # (%) patients collecting >5 × 106 CD34+ cells/kg in ≤2 apheresis days	% Switch from Poor to Good	Average Cost/pt	Average Cost/pt difference from reference cohort
A) VP-16/G-CSF [reference cohort]	0	90 (57%)	n/a	$20,184 (actual)	0 (reference)
B) G-CSF + plerixafor	159 (100%)	78 (49%)	n/a	$32,760	$12,576
C) VP-16/G-CSF + plerixafor (3 doses for all)	159 (100%)	159 (100%)	100% (breakeven not possible)	$32,924	$12,740
D) VP-16/G-CSF + plerixafor (3 doses for predicted poor mobilizers)	69 (43%)	**131 (82%)**	**62%** (breakeven)	$20,228	**$44**
E) VP-16/G-CSF + plerixafor (2 doses for all)	159 (100%)	159 (100%)	100% (breakeven not possible)	$26,924	$6,740
F) VP-16/G-CSF + plerixafor (2 doses for predicted poor mobilizers)	69 (43%)	**124 (78%)**	**49%** (breakeven)	$20,233	**$49**

A. All patients receive etoposide and G-CSF, with efficacy rates, costs and complications calculated from our observed cohort.

B. All patients receive G-CSF (7 total days) and 3 doses of plerixafor, 3 days of apheresis, no levofloxacin, no etoposide, no PRBC transfusions, no Platelet transfusions, no IV antibiotics, no inpatient admissions. Median doses of plerixafor, median days of apheresis, and efficacy rates are extrapolated from published phase III data.[2]

C. All patients receive etoposide and G-CSF. Median 3 doses of plerixafor are given to all patients. This scenario assumes a 100% efficacy rate in converting bad to good mobilizers. Average costs/pt based on costs associated with patients who are good mobilizers + 3 doses of plerixafor for each patient.

D. All patients receive etoposide and G-CSF. Median 3 doses of plerixafor are given to predicted poor mobilizers based on first CD34 count. A breakeven analysis is performed by modeling the # of patients who would need to experience improved outcomes and thus lower resource utilization in order to offset the costs of giving plerixafor to these patients. Please see Table 7 for component costs.

E. All patients receive etoposide and G-CSF. Median 2 doses of plerixafor are given to all patients. This scenario assumes a 100% efficacy rate in converting bad to good mobilizers. Average costs /pt based on costs associated with patients who are good mobilizers + 2 doses of plerixafor for each patient.

F. All patients receive etoposide and G-CSF. Median 2 doses of plerixafor are given to predicted poor mobilizers based on first CD34 count (probability ≤0.5). A breakeven analysis is performed by modeling the # of patients who would need to experience improved outcomes and thus lower resource utilization in order to offset the costs of giving plerixafor to these patients. Please see Table 5 for component costs.

Table 5

Component breakdown of average cost per patient in breakeven analyses (scenarios D and F in Table 6).

Component (average per patient costs)	Average cost of treatment with VP-16/G-CSF + 3 doses plerixafor for predicted poor mobilizers (Scenario D)				Average cost of treatment with VP-16/G-CSF + 2 doses plerixafor for predicted poor mobilizers (Scenario F)			
	Good	Poor	Total		Good	Poor	Total	
	N=131	N=28	N=159		N=124	N=35	N=159	
VP-16 (% contribution to total cost)	$310,564 (15.9%)	$66,380 (3.3%)	$376,944 (9.5%)		$293,969 (15.9%)	$82,975 (4.7%)	$376,944 (10.4%)	
G-CSF	$969,033 (49.6%)	$298,507 (14.9%)	$1,267,540 (32.0%)		$917,253 (49.6%)	$373,133 (21.0%)	$1,290,386 (35.6%)	
Plerixafor	-	$1,242,000 (62.1%)	$1,242,000 (31.4%)		-	$828,000 (46.6%)	$828,000 (22.8%)	
Mobilization/ collection	$492,666 (25.2%)	$285,860 (14.3%)	$778,526 (19.7%)		$466,340 (25.2%)	$357,324 (20.1%)	$823,665 (22.7%)	
Hospitalization	$9,577 (0.5%)	$12,773 (0.6%)	$22,350 (0.6%)		$9,066 (0.5%)	$15,966 (0.9%)	$25,032 (0.7%)	
MD/Nurse Visits	$5,131 (0.3%)	$6,052 (0.3%)	$11,184 (0.3%)		$4,857 (0.3%)	$7,566 (0.4%)	$12,423 (0.3%)	
Transfusions	$26,197 (1.3%)	$33,027 (1.7%)	$59,224 (1.5%)		$24,798 (1.3%)	$41,284 (2.3%)	$66,081 (1.8%)	
Antibiotics	$24,608 (1.3%)	$9,915 (0.5%)	$34,523 (0.9%)		$23,293 (1.3%)	$12,393 (0.7%)	$35,687 (1.0%)	
Other services/ drugs	$117,489 (6.0%)	$45,920 (2.3%)	$163,408 (4.1%)		$111,211 (6.0%)	$57,400 (3.2%)	$168,610 (4.6%)	
Total Cost (100%)	**$1,955,267 (100%)**	**$2,000,433 (100%)**	**$3,955,699 (100%)**		**$1,850,787 (100%)**	**$1,776,041 (100%)**	**$3,626,828 (100%)**	

Table 6

Comparison of Efficacy of Chemomobilization with Published Phase III Data

Parameter	VP + G (current sample) N = 159	G alone (published) N = 148	G + Plerixafor (published) N = 150
Median total $CD34^+$ cells × 10^6/kg N (range)	6.23 (0.0-27.6)	1.98 (0.06-15.0)	5.69 (0.03[6]-29.22[14])
Number of patients collecting ≥5 × 10^6CD34^+ cells/kg in ≤ 2 apheresis days (%)	89 (55.9%)	21 (14.2%)	74 (49.1%[6])[15]
Number of patients collecting ≥2 × 10^6CD34^+ cells/kg in ≤ 4 apheresis days (%)	131 (82.4%)	88 (59.8%)	138 (90.9%)
Number of patients proceeding to transplantation after initial mobilization (%)	151 (95%)	66 (45%)	135 (90.0%)