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An effective mobilization strategy for lymphoma patients after failed upfront mobilization with plerixafor

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Abstract

In an otherwise eligible patient, inadequate mobilization of PBSCs is a limiting factor to proceeding with an auto-ASCT. In such situations, plerixafor is commonly added to improve PBSC collection yields along with cytokine (G-CSF alone) or chemomobilization (chemotherapy +G-CSF). Individually, both strategies are proven to be safe and effective. Here we report six patients who underwent successful mobilization with combination chemomobilization plus plerixafor after upfront failure of cytokine mobilization plus plerixafor. The median CD34⁺ cell yield after chemomobilization was $2.48 \times 10^6/\text{kg}$ (range 0.99–8.49) after receiving one to two doses of plerixafor. All patients subsequently underwent ASCT without major unforeseen toxicities and engrafted successfully. No significant delays in time to neutrophil recovery were observed. Our experience highlights the safety and effectiveness of chemomobilization with plerixafor after G-CSF plus plerixafor (G+P) failure and suggests this is a viable salvage strategy after initial failed G+P mobilization.

INTRODUCTION

Auto-SCT is an important and potentially curative therapy for patients with relapsed lymphoma; however, 5–40% of lymphoma patients fail to mobilize adequate numbers of PBSCs, and thus cannot undergo a therapy that is known to improve long-term survival.¹ Over the past decade, different strategies have been implemented to achieve adequate apheresis yields for successful engraftment. These strategies include cytokine growth factors, either alone or in combination with chemotherapy and, more recently, the partial CXC chemokine receptor-4 antagonist, plerixafor.^{2,3}

Plerixafor disrupts the stromal cell-derived factor-1/CXCR4 interaction and reduces the binding and chemotaxis of hematopoietic stem cells to the BM stroma.^{4,5} Mobilization with G-CSF plus plerixafor (G+P) is an Food and Drug Administration-approved strategy for

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PBSC mobilization before ASCT in patients with non-Hodgkin lymphoma or multiple myeloma.^{6–8} This indication is based on two phase III, double-blind, randomized clinical studies in which combination G+P mobilized more hematopoietic stem cells in fewer apheresis sessions compared with G-CSF alone in MM and non-Hodgkin lymphoma patients.^{4,9–11} The combination of G+P has been shown to improve PBSC collection yields and potentially reduce mobilization failure rates.^{12–15} Of patients undergoing upfront utilization of G+P, 14% failed to achieve more than 2×10^6 CD34⁺ cells/kg.⁴ Despite utilization of upfront G+P, there remains a subset of patients unable to collect adequate stem cells.

In addition, G+P after chemotherapy as a front-line mobilization strategy safely and effectively allows the collection of an adequate number of PBSCs in order to perform ASCT in MM and lymphoma.^{16–18} Previous reports have outlined mobilization algorithms including a strategy to include plerixafor for poor mobilizers.¹⁹ However, there has not been a report outlining a successful collection strategy after failed G+P mobilization. We report on six patients with relapsed or refractory lymphoma who were deemed eligible for ASCT and subsequently underwent chemomobilization with the addition of plerixafor following failure of upfront mobilization with G+P between January 2012 and April 2013. Patients were eligible for inclusion if they failed to yield 2×10^6 stem cells/kg following initial mobilization attempt with G+P. Patients who failed initial mobilization following chemotherapy plus G+P were not included. All patient data were collected prospectively with informed consent and approval from the institutional review board at the Ohio State University. Here we describe our institution's experiences and propose this option as a viable strategy in poor mobilizers who fail initial cytokine and plerixafor mobilization. The feasibility and efficacy of such a strategy has not been reported to our knowledge.

MATERIALS AND METHODS

This study is an institutional review board-approved descriptive case series of six consecutive patients who underwent chemomobilization with the addition of plerixafor following failure of mobilization with upfront G+P. Given the small sample size, descriptive statistics with a median and a range were used to summarize the time to neutrophil and platelet engraftment. Collection outcomes were described on an individual patient basis.

The target optimal CD34⁺ cell yield at our institution is at least 5×10^6 /kg recipient body weight, whereas a minimum dose of at least 2×10^6 /kg is recommended to proceed with ASCT. Our institutional standard is to add plerixafor on day 4 of G-CSF mobilization for patients who received radiation, 10 or more cycles of chemotherapy, are aged 60 or older or on day 5 for patients who had a CD34⁺ cell count of $<10/\mu\text{L}$ that morning. After an unsuccessful attempt at mobilization with G+P (1–2 doses), these six individuals underwent chemomobilization with either cyclophosphamide (CY; 3 gm/m²) or etoposide 2000 mg/m² (VP-16) at the discretion of the treating physician. G-CSF (10 µg/kg) was started on day 5 after chemotherapy. Plerixafor (0.24 mg/kg) was administered to patients who were in danger of failing to mobilize, with WBC recovery but persistently low levels of circulating CD34⁺ cells after chemotherapy. In both approaches, plerixafor was administered the evening before planned apheresis. Once the peripheral blood CD34⁺ count was $10/\mu\text{L}$,

apheresis was done using a Caridian Cobe Spectra machine (Terumo, Lakewood, CO, USA) and four blood volumes were processed according to institutional guidelines.

All patients were initially treated in a HEPA-filtered inpatient BMT unit and received fungal and herpes zoster prophylaxis as appropriate. Thawed autologous stem cells were infused through a central venous catheter on day 0 following conditioning chemotherapy. All patients received BEAM conditioning (carmustine, 300 mg/m² on day – 6; etoposide, 100 mg/m² and cytarabine, 100 mg/m² twice daily on days – 5 through – 2; and melphalan, 140 mg/m² on day – 1). All patients received irradiated and leukoreduced blood products. Post-transplant G-CSF was administered at 5 µg/kg per day starting on day +1 for patients who underwent transplant before November 2012 and starting on day +7 for patients who underwent transplant afterward. Neutrophil engraftment was defined as the first of three successive days with an absolute neutrophil count $0.5 \times 10^9/L$ after post-transplant nadir, and platelet engraftment was defined as the first of three successive days with a platelet count $20 \times 10^9/L$ without platelet transfusion.

RESULTS

Baseline characteristics of the six patients are shown in Table 1. For five of the six patients, chemomobilization+plerixafor was the second mobilization attempt. For patient #1, this was the third attempt after failed attempts at mobilization of chemotherapy with rituximab, ifosfamide, carboplatin, and etoposide (RICE) and subsequently G+P. The median age was 55 (range, 38–68). Five of the six patients were female. One had Hodgkin's lymphoma, four had diffuse large B-cell lymphoma, and one had grade 3A follicular lymphoma. The patient with follicular lymphoma had stable disease going into collection. All of the other patients had chemosensitive disease, with a partial response²⁰ or better following their most recent salvage. Karnofsky performance status ranged from 70 to 90, and the median comorbidity index was 3.5 (range, 0–9). The median number of prior therapies was 3, the median number of cycles of chemotherapy received was 10 (range, 8–14) and two of the six patients had received radiation. There were no patients with BM involvement by their lymphoma.

Table 2 describes the results of PBSC mobilization with G+P and salvage mobilization in all six patients. The median peak peripheral blood CD34⁺ cell count obtained during G+P mobilization was 7/µL (range, 6–20). The median CD34⁺ cell count after salvage mobilization was 15.5/µL (range, 14–105). The median CD34⁺ cell yield after salvage mobilization was $2.48 \times 10^6/kg$ (range, $0.99-8.49 \times 10^6$) receiving one to two doses of plerixafor. One patient (#3) had already yielded $1.42 \times 10^6/kg$ during his previous G+P mobilization, so an additional $0.99 \times 10^6/kg$ provided an adequate number to move forward with ASCT. All six patients received high dose therapy with BEAM. One patient (#1) received 100 mg/m² of melphalan. The median time to neutrophil engraftment was 12 days (range, 9–13). The median time to platelet recovery was 13.5 days (range, 10–24). All six patients are alive and without disease progression at a median follow-up of 231 days (range, 29–622).

DISCUSSION

Although not inexpensive, plerixafor has provided many patients with the opportunity to collect an adequate number of stem cells for ASCT who otherwise would be deprived of a potentially life saving treatment. Plerixafor combined with G-CSF or plerixafor combined with chemomobilization have each shown to be effective mobilization strategies.²¹ A debate continues regarding when each strategy should be used. Our approach at Ohio State, highlights a safe and effective approach applicable to all individuals (Figure 1).²² However, it more importantly highlights an effective strategy to mobilize patients who have failed mobilization, as well as those with risk factors for collection failure. Thanks to employment of this strategy, mobilization failure is not a significant barrier to proceeding with ASCT at our institution.

In this case series, we examined the utility of adding plerixafor to chemomobilization in patients who failed mobilization with upfront G+P. We found that all six patients were successfully mobilized following either CY or VP-16 with the addition of G+P. Interestingly, one patient (#1) failed collection with initial chemomobilization, and then failed G+P, but was ultimately successfully mobilized after VP-16 and G+P. This patient highlights the superiority of adding plerixafor to chemomobilization.

Although our patients did not have overwhelming risk factors for poor mobilization rates, they did have notable risk factors including increasing age, prior radiotherapy and multiple prior lines of intensive therapy as listed in Table 1.⁵ None of our patients had BM involvement or directly BM toxic therapy. Fortunately, in this cohort, all of our patients successfully underwent ASCT with only slight delay in engraftment, which is not unexpected, given the lower infused cell doses. At last follow-up, all of our patients were without progression of their disease. Other groups have reported inferior ASCT outcomes in patients who mobilized poorly.^{23–25} This has not been our experience with this small number of patients, but our follow-up is short.

We acknowledge the small sample size, the need for further validation, the inherent bias of our retrospective analysis and the heterogeneity among patients as limitations of this study. Despite these limitations, it appears that chemomobilization with G+P is an effective option in patients who have previously failed to mobilize with G+P. In addition, there is a void of published patients treated with this approach and as the age of patient eligibility continues to be pushed higher, this strategy seems to be a viable option in lymphoid malignancies and certainly warrants further exploration in the elderly with multiple myeloma.

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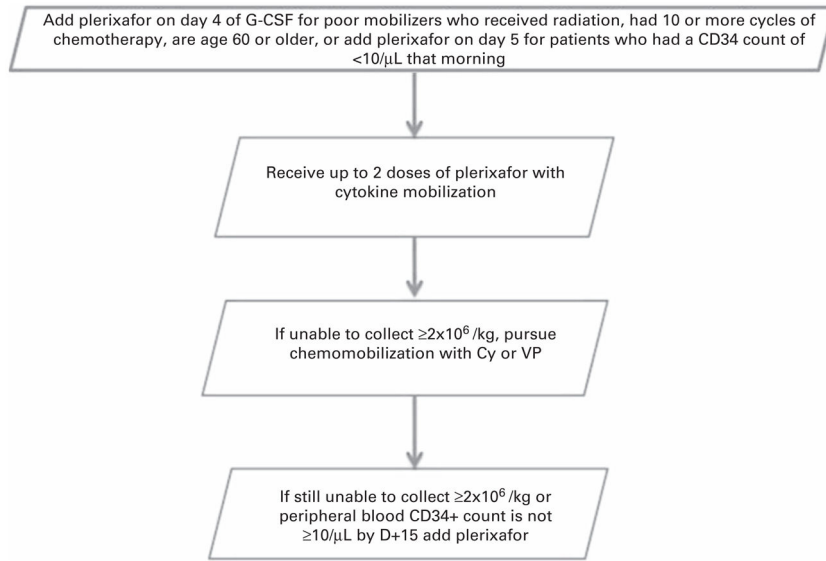


Figure 1.
Flow chart on an effective mobilization strategy based on our single institution experience.

Table 1
Demographics of six patients who underwent chemomobilization with G-CSF plus plerixafor

Patient	Sex	Age at mobilization (year)	Diagnosis	Stage	CMI	Disease status	Total mob attempts	Number of prior therapies	Prior radiation	Prior therapies
1	F	62	DLBCL	3A	9	PR2	3	3	No	RITx5; RCEPPx6; RICEx3
2	F	40	DLBCL	2A	5	CR1r	2	2	No	RCHOPx8; RICEx2
3	M	38	FL (G3)	3A	4	SD	2	3	Yes	RCHOPx6; XRT; RESHAPx4; REPOCHx4
4	F	65	cHL	2A	0	CR2	2	4	Yes (M)	ABVDx1; MOPP; XRT; ICE
5	F	48	DLBCL	3B	3	CR2	2	2	No	RCHOPx6; RICEx2
6	F	68	DLBCL	4A	2	CR2	2	3	No	RCHOPx6; RICEx1; RGenOx x3

Abbreviations: CMI = comorbidity index; DLBCL = diffuse large B-cell lymphoma. CR1r indicates that patient initially had refractory disease to RCHOP but responded to salvage RICE, was in CR before SCT (M) mediastinal involvement. Prior therapies include RIT (rituximab); RCEPP (cyclophosphamide, etoposide, procarbazine, prednisone); RICE (rituximab, ifosfamide, carboplatin, etoposide); RCHOP (rituximab, cyclophosphamide, doxorubicin, prednisone); XRT (radiation); RESHAP (rituximab, etoposide, methylprednisolone, cisplatin, cytarabine); REPOCH (rituximab, etoposide, prednisone, vincristine, doxorubicin); ABVD (doxorubicin, bleomycin, vinblastine, decarbazine); MOPP (nitrogen mustard, vincristine, procarbazine, prednisone); RGenOx (rituximab, gemcitabine, oxaliplatin).

Table 2

Results of PBSC mobilization with G-CSF+plerixafor and salvage mobilization in all six patients

Patient	No of prior doses of plerix during G+P mobilization	Peak PB CD34 during G+P mobilization	Chemo-mobilization	No of plerix after chemo-mobilization	Day of first plerix after chemo-mobilization	Day 1st collection after chemo-mobilization+plerix	Peak PB CD34 after chemo-mobilization+plerix	No of apheresis sessions	TNC $\times 10^8/\text{kg}$	CD34+ $\times 10^6/\text{kg}$ yield	Total CD34 infused	Days to neutrophil, platelet recovery	PFS since SCT (days)
1	2	7	VP	2	20	21	16	2	5.73	2.34	2.34	10, 18	622
2	2	6	VP	1	16	17	105	1	7.58	8.49	8.49	9, 13	302
3	2	20 ^a	CY	2	14	15	14	2	4.71 ^b	0.99	2.41	12, 10	224
4	1	8	VP	2	15	16	15	2	6.81	2.02	2.02	13, 24	238
5	2	8	CY	2	17	18	18	2	6.25	3.61	3.61	12, 12	33
6	2	7	CY	2	19	20	14	3	6.69	2.62	2.62	12, 14	29

Abbreviation: CY =cyclophosphamide 3 gm/m²; VP = VP-16 or etoposide 2000 mg/m²; G+P =G-CSF plus plerixafor.

^aYielded $0.71 \times 10^6/\text{kg}$ PBSCs on two apheresis sessions.

^bYielded an additional $2.96 \pm 3.96 \times 10^8/\text{kg}$ TNCs previously.