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Autologous

Etoposide + Granulocyte Colony-Stimulating Factor and Optional Plerixafor in Patients Who Failed Chemomobilization with or without Plerixafor

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A B S T R A C T

We conducted a retrospective study of 62 patients undergoing etoposide (2 g/m^2) + granulocyte colony-stimulating factor (G-CSF; 10 patients also received additional plerixafor) as a salvage stem cell mobilization regimen after previous unsuccessful chemomobilization with or without plerixafor. The median peak CD34$^+$ values after etoposide + G-CSF ± plerixafor was 54.07 CD34$^+$/μL compared with 9.6 CD34$^+$/μL after previous mobilization attempts ($P < .001$). The median yield was 6.33×10^6 CD34$^+$ cells/kg per 2 apheresis. Etoposide + G-CSF ± plerixafor mobilization regimen resulted in 91.53% successful mobilizations and 89.83% of patients proceeding to autologous stem cell transplantation. All 7 patients who had previously failed plerixafor-based mobilization attempts were successfully mobilized with etoposide + G-CSF ± plerixafor and proceeded to autologous stem cell transplantation. The most common grades 3 to 4 adverse events of etoposide + G-CSF ± plerixafor were febrile neutropenia (69.35%), mucositis (51.62%), and bacteremia (20.97%). No fatal outcomes were observed. Rates of 12-month overall survival and progression-free survival were 88.71% and 70.97%, respectively. Etoposide + G-CSF ± plerixafor is an effective regimen for salvage stem cell mobilization also in patients who failed plerixafor, with most patients undergoing autologous stem cell transplantation. The adverse event rate may warrant a decrease in the dose of etoposide.

INTRODUCTION

Autologous stem cell transplantation (ASCT) is an effective procedure for the treatment of various oncologic and hematologic malignancies and autoimmune diseases. Hematopoietic CD34$^+$ stem cells can be harvested either directly from the bone marrow or collected via apheresis from peripheral blood, which is usually the preferred source of stem cells for ASCT. An accepted indicator to start the peripheral blood stem cell (PBSC) apheresis is the value of >10 to 20 CD34$^+$ cells/μL in the peripheral blood [1-3]. The current minimal amount of CD34$^+$ cells needed to achieve a fast, complete, and stable long-term engraftment of PBSCs has been determined as ≥2 to 2.5×10^6 CD34$^+$ cells/kg for a single ASCT [4]. Chemomobilization with high-dose cyclophosphamide (usually 2 to 4 g/m^2) + granulocyte colony-stimulating factor (G-CSF) is widely used because of its safety and efficacy [5-7].

Alternative regimens to mobilize PBSCs include Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (CHOP/HiCHOP), high-dose cytarabine, Ifosfamide, Carboplatin, Etoposide (ICE), Dexamethasone, High Dose Cytarabine, Cisplatin (DHAP), and high-dose etoposide [8-15]. Despite various options, 10% to 20% of patients fail to achieve sufficient CD34$^+$ values to start apheresis or to collect an adequate number of CD34$^+$ cells to ensure engraftment [16-29]. The introduction of plerixafor has offered a novel approach for poor mobilizers [16-25]. However, there is no standard mobilization procedure for patients who fail their first mobilization attempt, especially after administration of plerixafor. In this article we present the efficacy and safety of etoposide (VP-16) + daily G-CSF + optional plerixafor as a second-line PBSC mobilization regimen in both plerixafor-naïve patients and plerixafor failures.

METHODS

Patient Characteristics and Statistical Methods

We retrospectively reviewed the clinical data of patients who underwent stem cell mobilization with VP-16 + G-CSF + optional plerixafor (VP-16 + G-CSF ± plerixafor) between 2004 and 2016 at the Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania (Figure 1). Inclusion criteria were patients receiving

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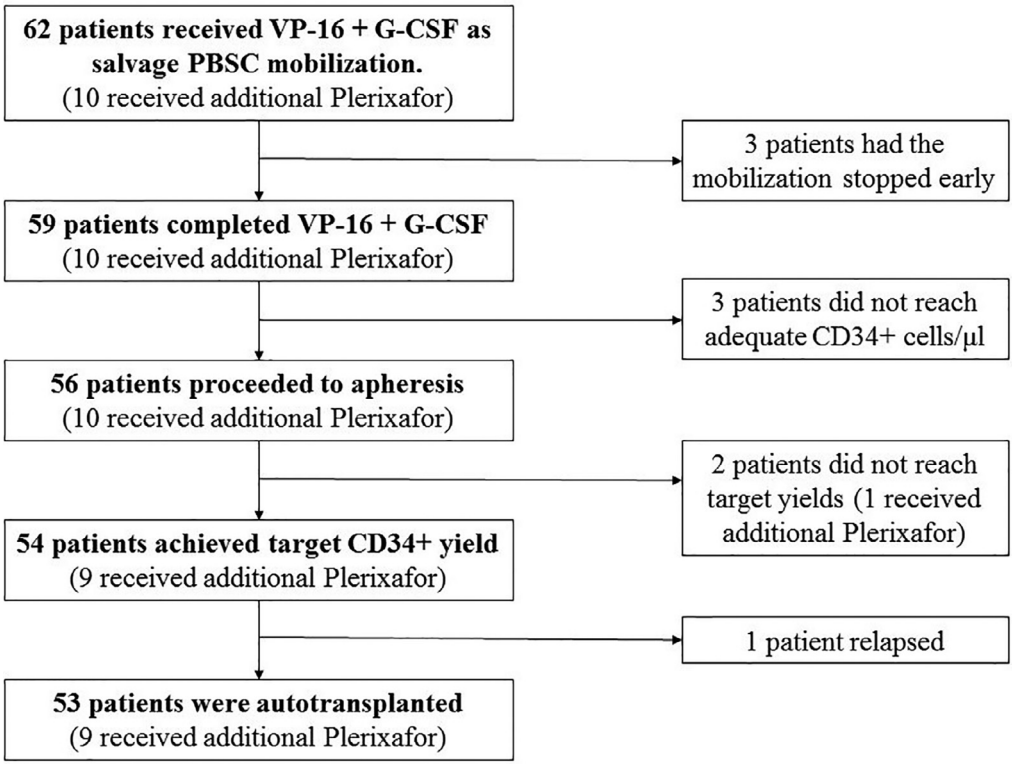

Figure 1. Patients mobilized with VP-16 + G-CSF ± plerixafor.

VP-16 + G-CSF ± plerixafor as salvage PBSC mobilization regimen with or without additional plerixafor after previous mobilization failures and age ≥ 18 years. Mobilization failure was defined as either a failure to collect a total of 2×10^6/kg $CD34^+$ cells or the number of $CD34^+$ cells below the threshold to start leukapheresis according to the center policy set at >20 $CD34^+$ cells/μL in the peripheral blood.

The primary endpoint was the number of patients undergoing ASCT after salvage VP-16 + G-CSF ± plerixafor mobilization. Secondary endpoints were maximum $CD34^+$ values (compared with maximum $CD34^+$ values of previous PBSC mobilization attempts), total number of collected $CD34^+$ cells, number of apheresis cycles, time from the start of mobilization to the first leukapheresis, and 12-month overall survival and progression-free survival after mobilization. To evaluate the toxicity profile of our mobilization regimen, we analyzed time to hematologic recovery (platelet [PLT] count and absolute neutrophil count [ANC]), number of transfusions (RBC, PLT, and plasma components), and grades 3 to 5 nonhematologic adverse events according to Common Terminology Criteria of Adverse Events v4.02 scale.

Descriptive statistics were used for safety and efficacy analysis. The difference between maximum $CD34^+$ values was evaluated using the Mann-Whitney U test. Difference with $P < .05$ was considered statistically significant. Adverse events and 12-month overall survival and progression-free survival were analyzed in the intention-to-treat (ITT) population. This study was approved by the Vilnius Regional Biomedical Research Ethics Committee (approval no. 158200-18/4-1032-528).

Mobilization and Leukapheresis

The salvage chemomobilization regimen consisted of VP-16 2 g/m^2 (500 mg/m^2 2-hour i.v. infusion on days 1 to 4) + G-CSF 10 μg/kg/day s.c. usually from day 7 until the last day of leukapheresis. In 2 cases VP-16 was given at a reduced dose of 1.5 g/m^2 (.375 g/m^2 on days 1 to 4) because of baseline renal insufficiency. One or 2 doses of plerixafor (.24 mg/kg s.c.) were used in patients with marginal $CD34^+$ values (usually 10 to 25 $CD34^+$ cells/μL) or insufficient $CD34^+$ yields. Of note, plerixafor was registered in the European Union only in 2009, and thus a small number of patients were remobilized with VP16 + G-CSF before the plerixafor era.

Patients were hospitalized during mobilization. Adequate hydration (1.5 to 2 L/m^2), antiemetic prophylaxis, and premedication with ondansetron 16 mg i.v. twice daily, diphenhydramine 25 mg i.v. daily, and dexamethasone 8 mg i.v. daily was routinely administered on days 1 to 4. Ciprofloxacin 500 mg twice a day was given for antibacterial prophylaxis during agranulocytosis (ANC < 1×10^9/l), sulfamethoxazole-trimethoprim 960 mg 2 times a day twice a week for pneumocystis prophylaxis, and valacyclovir 500 mg twice daily for herpes virus prophylaxis. PLT transfusions were indicated when PLT level dropped below 20×10^9/L or 50×10^9/L (if interventions like central venous catheter implantation were necessary). RBC transfusions were administered to keep hemoglobin levels above 80 g/L.

The threshold to start leukapheresis was usually when >20 $CD34^+$ cells/μL in the peripheral blood; however, in a few cases the threshold was lower. The policy of a higher $CD34^+$ cells/μL threshold is based on a smaller number of apheresis needed (our goal is to collect target $CD34^+$ numbers in 1 or 2 apheresis) resulting in reduced volumes of apheresate and lower cumulative DMSO dose during ASCT. Collected cells were cryopreserved using DMSO and stored in liquid nitrogen. The target yield of cryopreserved $CD34^+$ cells was $>2 \times 10^6$ $CD34^+$/kg.

RESULTS

Patients

Sixty-two patients with oncologic and hematologic diseases who underwent a second-line (60) or third-line (2) hematopoietic stem cell mobilization with VP-16 + G-CSF ± plerixafor were enrolled (ITT group). Fifty-two patients (83.9%) were remobilized only with VP-16 + G-CSF, whereas the remaining 10 patients (16.1%) were given an additional 1 or 2 doses of plerixafor because of their marginal $CD34^+$ values or insufficient $CD34^+$ yields. Mobilization was stopped in 3 patients because of disease progression (n = 1), septic shock (n = 1), and acute kidney injury after the third dose of etoposide (n = 1). These 3 patients were excluded from the per-protocol analysis (59 patients). Patient characteristics are summarized in Table 1.

The median age was 59 years (range, 29 to 76), and there were more women (1.29 females/males). The most common underlying disease was Hodgkin/non-Hodgkin lymphoma (N30), followed by multiple myeloma (N28). Of 30 lymphoma patients, 24 (80%) had stage IV disease and 6 (20%) stage III disease. Fifty-five percent of patients (N34) had previously received 1 line of chemotherapy before proceeding to ASCT; others were more pretreated with 2 (N22), 3 (N5), or 4 lines

Table 1
Patient Characteristics (N = 62)

Characteristic	Value
Gender	
Women	35 (56.45)
Men	27 (43.55)
Age	
Median, yr (range)	59 (29-76)
Diagnosis	
Hodgkin/non-Hodgkin lymphoma	30 (48.39)
Multiple myeloma	28 (45.16)
Acute leukemia	2 (3.23)
Amyloidosis	1 (1.61)
Yolk sack tumor	1 (1.61)
Previous unsuccessful mobilizations	
One	58 (93.55)
Two	4 (6.45)
Previous mobilization regimens	
Cyclophosphamide 2 g/m^2 + G-CSF	26 (38.46)
Cyclophosphamide 3 g/m^2 + G-CSF	6 (9.62)
Cyclophosphamide 4 g/m^2 + G-CSF	20 (34.62)
HiCHOP + G-CSF	2 (3.85)
DHAP + G-CSF	4 (5.77)
ICE + G-CSF	1 (1.92)
TI (paclitaxel, ifosfamide) + G-CSF	1 (1.92)
VTD-PACE + G-CSF	1 (1.92)
HDAraC + G-CSF	1 (1.92)
G-CSF only	4 (5.77)

Values are n (%) unless otherwise defined.
HiCHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone. DHAP: Dexamethasone, High Dose Cytarabine, Cisplatine. ICE: Ifosfamide, Carboplatin, Etoposide. VTD-PACE: Bortezomib, Thalidomide, Dexamethasone, Cisplatin, Doxorubicine, Cyclophosphamide, Etoposide. HDAraC - High Dose Cytarabine.

(N1). All patients were in complete or partial remission and were suitable for ASCT. Before salvage PSBC mobilization with VP-16, patients had undergone unsuccessful PBSC mobilization using various regimens, mostly cyclophosphamide + G-CSF. Seven patients had failed mobilization of chemotherapy and plerixafor (plerixafor failures).

Mobilization and Transplantation

In the per-protocol analysis, the median peak CD34$^+$ values in peripheral blood after VP-16 + G-CSF ± plerixafor were 54.07 CD34$^+$/μL (range, 1.96 to 665.71) versus 9.6 CD34$^+$/μL (range, .35 to 71.46) after previous PBSC mobilization regimens ($P < .001$) (Figure 2). In several cases patients reached adequate CD34$^+$ values in the peripheral blood during the first line mobilization; however, their target collection yield was not sufficient for tandem ASCTs. These attempts were considered unsuccessful, and salvage PBSC mobilization with VP-16 + G-CSF ± plerixafor was administered. In a subgroup analysis the median peak CD34$^+$ value in the peripheral blood after VP-16 + G-CSF + plerixafor (10 patients) was 33.16 CD34$^+$/μL (range, 13.76 to 61.96) compared with 64.36 CD34$^+$/μL (range, 1.96 to 665.71) in 49 patients who were remobilized with VP-16 + G-CSF without additional plerixafor. The harvesting results after VP-16 + G-CSF ± plerixafor are summarized in Table 2.

The median yield in the per-protocol group was 6.33×10^6 CD34$^+$ cells/kg (range, .47 to 26.68). The median number of apheresis per patient was 2 (range, 1 to 4). The first apheresis was performed on median day 19 (range, 15 to 45) from the start of VP-16. In 34 of 59 patients (57.63%) at least 5×10^6 CD34$^+$ cells/kg were collected. Rates of 1-year progression-free survival and overall survival after VP-16 + G-CSF ± plerixafor mobilization were 70.97% and 88.71%, respectively (ITT analysis).

Proportion of Patients Undergoing ASCT

Of 59 patients who had completed the scheduled VP-16 + G-CSF ± plerixafor mobilization regimen (10 received additional plerixafor), 3 patients never reached sufficient CD34$^+$ counts, and thus the aphereses were not performed. Plerixafor was not administered to these patients because maximum CD34$^+$ values were only 6.5, 4.8, and 1.96 CD34$^+$ cells/μL. Two patients reached minimal CD34$^+$ values suitable for apheresis; however, the collected PBSC count was too low for ASCT ($.47 \times 10^6$ and $.97 \times 10^6$ CD34$^+$ cells/kg, respectively). One patient did not receive additional plerixafor because her CD34$^+$ values peaked only at 7.17 CD34$^+$ cells/μL, and the decision to start apheresis was debatable. In the other case additional plerixafor was used at a value of 13.76 CD34$^+$ cells/μL, which unfortunately dropped to 7.31 CD34$^+$ cells/μL the next day, and apheresis was abandoned. This was the only failure of VP-16 + G-CSF + plerixafor regimen. In the remaining 9 cases additional plerixafor increased the CD34$^+$ values, and target CD34$^+$ yields were achieved. Overall, 54 patients (ITT, 87.1%; per-protocol, 91.53%) underwent successful PBSC mobilization and harvest ($>2 \times 10^6$ CD34$^+$ cells/kg). One patient relapsed after successful PBSC harvest, resulting in total of 53 patients (ITT, 85.48%; per-protocol, 89.81%) proceeding to ASCT. Details are presented in Table 3.

Engraftment after ASCT

In 53 transplanted patients, granulopoiesis regeneration (ANC > .5) was observed on median day 11 (range, 9 to 39) after ASCT with G-CSF support from day 5. Fifty-two of 53 patients reached ANC > .5 by day +21. One patient required an additional CD34+ boost (5×10^6 CD34$^+$ cells/kg) on day +23 with granulopoiesis recovery on day +39. PLT recovery (PLT > 50×10^9/L) was observed on median day 39 (range, 12 to 226) in assessable patients. This delay was due to patients being routinely discharged before the PLT recovery $>50 \times 10^9$/L and retrievable blood counts were performed only during the follow-up visits.

VP-16 + G-CSF after Plerixafor-Based Mobilization Failures

In a subgroup of 7 patients who had previously underwent unsuccessful mobilizations using plerixafor, all 7 (100%) achieved both target CD34$^+$ values (median peak value, 76.26 CD34$^+$/μL [range, 38.57 to 119.6]) and adequate PBSC harvests (median, 5.41×10^6 CD34$^+$ cells/kg [range, 2.29 to 10.46]) after VP-16 + G-CSF mobilization (Table 3). In plerixafor-naïve patients median peak CD34+/μL value was 50.93 (range, 1.96 to 665.67) and median yield 6.62×10^6 CD34$^+$ cells/kg (range, .47 to 26.68).

Only 1 plerixafor failure required a single dose of additional plerixafor during VP-16 + G-CSF because the CD34$^+$ yield was too low after the first apheresis ($.66 \times 10^6$ CD34$^+$ cells/kg). All 7 patients were autotransplanted and achieved durable engraftment. Two of 7 patients had previously failed 2 attempts to mobilize PBSCs with different regimens. One of these 2 patients had received plerixafor during both previous unsuccessful mobilization attempts; however, after a third-line mobilization with VP-16 + G-CSF, plerixafor was not used because of high CD34$^+$ values and a high yield (10.46×10^6 CD34$^+$ cells/kg) after a single apheresis. The details are presented in Table 4.

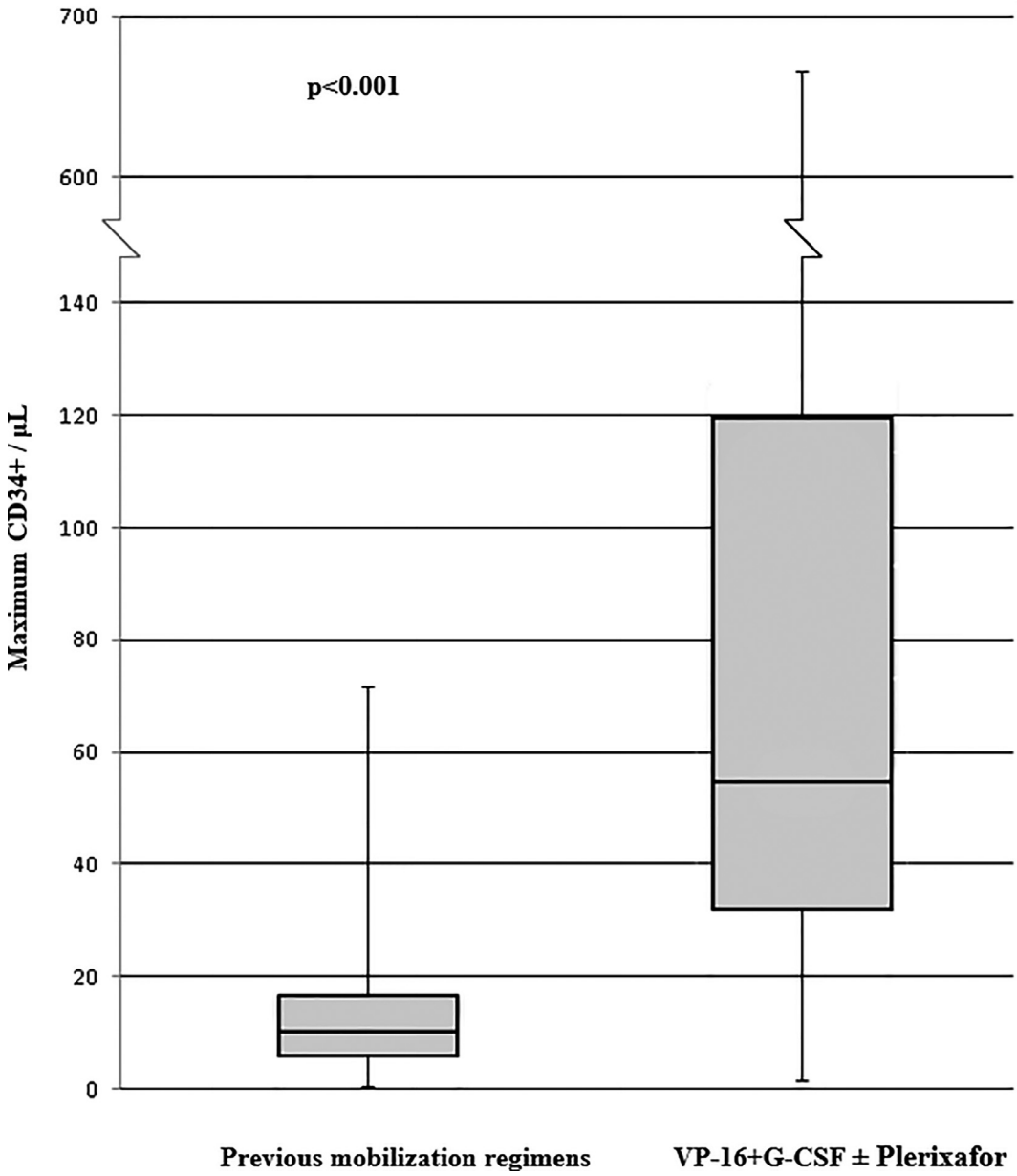

Figure 2. Maximum $CD34^+$ values.

Table 2
Harvest Results

Charateristic	Median ()
Day of first apheresis	19 (15-45)
Number of aphereses	2 (1-4)
Collected $CD34^+$, mL/kg	6.33 (.47-26.68)

Safety and Toxicity

Adverse events are summarized in Table 5. Because of significant myelotoxicity of VP-16, febrile neutropenia, mucositis, and bacteremia were the most common adverse events in our group. Other complications were urinary tract infections, herpes infection, and flu. Serious adverse events (septic shock and

Table 3
Mobilization Efficacy

	ITT Analysis		Per-Protocol Analysis		Plerifaxor Failures	
Endpoint	N/n	Percentage	N/n	Percentage	N/n	Percentage
VP-16 + G-CSF mobilization completed	59/62	95.16	59/59	100	7/7	100
Apheresis started	56/62	90.32	56/59	94.92	7/7	100
PBSC yield was $>2 \times 10^6$ $CD34^+$/kg	54/62	87.1	54/59	91.53	7/7	100
Underwent ASCT	53/62	85.48	53/59	89.83	7/7	100

Table 4
Plerixafor Failures

			Preceding Unsuccessful Mobilization						VP-16 + G-CSF ± Plerixafor		
	Age (yr)	Disease	Regimen	Plerixafor Doses	$CD34^+$ cells/μL at which Plerixafor Was Administered	Peak $CD34^+$ cells/μL	$CD34^+$ Yield*	Time Interval Between Mobilizations† (days)	Peak $CD34^+$ cells/μL	Plerixafor	$CD34^+$ Yield*
1	64	DLBCL	HiCHOP + G-CSF	0	N.A.	9.36	N.A.	52	38.57	No	3.65
			Cy 4 g/m^2 + G-CSF + plerixafor	1	3.84	10.16	N.A.				
2	62	FCL	ICE + G-CSF + plerixafor	1	2.75	8.43	N.A.	91	119.6	No	6.21
3	66	MCL	Cy 4 g/m^2 + G-CSF + plerixafor	1	4.14	11.74	N.A.	93	117.74	No	10.46
			G-CSF + plerixafor	1	10.98	10.98	N.A.				
4	55	MM	Cy 2 g/m^2 + G-CSF + plerixafor	1	13.36	35.69	.72	49	96.57	No	7.97
5	38	HL	DHAP + G-CSF + plerixafor	2	21.19 and 21.81	21.81	1.71	93	76.26	No	3.58
6	59	MM	Cy 2 g/m^2 + G-CSF + plerixafor	2	13.62 and 19.35	19.35	.77	41	41.03	No	5.41
7	51	DLBCL	DHAP + G-CSF + plerixafor	1	19.55	25.22	.57	56	50.93	Yes	2.29

DLBCL indicates diffuse large B cell lymphoma; MM, multiple myeloma; MCL, mantle cell lymphoma; FCL, follicular lymphoma; HL, Hodgkin lymphoma; Cy, cyclophosphamide.
* In $CD34^+ \times 10^6$/kg after cryopreservation.
† Time interval between the start of preceding unsuccessful mobilization and VP-16 + G-CSF ± plerixafor.

Table 5
Adverse Events (N = 62)

Adverse events	No. of patients	Percentage
Febrile neutropenia	43	69.35
Positive blood cultures	13	20.97
Mucositis	32	51.62
Acute renal failure	2	3.23
Pneumonia	3	4.84
Other complications	4	6.45
Septic shock	2	3.23
Lethal outcomes	0	0

transfer to the intensive care unit) were reported in 2 cases. No fatal outcomes were observed.

Hematologic toxicity was manageable. Severe neutropenia (ANC $< .5 \times 10^9$) lasted for a median of 10 days (range, 4 to 23). Granulopoiesis regeneration (ANC $> .5 \times 10^9$/L) was observed on median day 18 (range, 15 to 28) after VP-16 + G-CSF. PLT regeneration was assessable in 27 of 59 patients (26 patients lacked information about the exact date and number of PLT transfusions or the date of PLT regeneration, and 6 patients had baseline thrombocytopenia before VP-16 + G-CSF). In assessable patients, the median duration of thrombocytopenia PLT $< 50 \times 10^9$/L was 7.5 days (range, 1 to 19) and PLT regeneration $> 50 \times 10^9$/L was observed on median day 20 (range, 16 to 32). Complete data about PLT transfusions were available in 33 patients: 30 (90.9%) required PLT transfusions with a median of 6 (range, 1 to 27) transfusions per patient. Complete data about RBC transfusions were available in 55 patients: 35 (63.64%) required RBC transfusions with a median of 2 (range, 1 to 7) transfusions per patient. One patient required a cryoprecipitate transfusion.

DISCUSSION

Second-line PBSC mobilization, especially in chemomobilization failures, remains a debatable topic among transplant physicians. Currently, plerixafor remains the main option for salvage PBSC mobilization, and its efficacy was evaluated in several studies [16-25]. The results were heterogeneous: The percentage of patients who underwent successful harvesting ($>2 \times 10^6$ $CD34^+$/kg) after second-line mobilization with plerixafor + G-CSF ranged from 37% to 100%, and the percentage of patients who proceeded to ASCT was 17% to 100%. The worst results were achieved in those patients who previously had failed chemomobilization. Despite diverse efficacy in chemomobilization + G-CSF failures as well as its high price, plerixafor remains a widely used option in remobilization strategies. Several single-center studies reported different salvage PBSC regimens without the addition of plerixafor in mobilization failures (Table 6).

Reiser et al. [28] presented data on 16 patients previously failing cyclophosphamide + G-CSF first-line mobilization who were successfully remobilized with VP-16 (2 g/m^2) + G-CSF, with most proceeding to ASCT. Our results support the findings of Reiser et al. in a larger population of patients with higher median age and also importantly in plerixafor failures. Ozkan et al. [9] reported data on lymphoma patients who were mobilized using VP-16 (1.6 g/m^2) + G-CSF of which a small group of 12 patients were chemomobilization failures. Only 6 of 12 (50%) were successfully remobilized with VP-16 + G-CSF achieving target $CD34^+$ yields. Another retrospective study by Calderon-Cabrera et al. [29] reported 33 patients receiving salvage mobilization regimen of intermediate-dose cytarabine + G-CSF with an

Table 6
Studies of Salvage Stem Cell Mobilization

Reference	No. of patients	Median Age (range) (yr)	Diagnosis	Salvage Mobilization Regimen	Additional Plerixafor	Proportion with Target $CD34^+$ Yield	Proportion Proceeding to ASCT	Previous Mobilization Regimen	No. of Plerixafor Failures
Ozkan et al. [9]	12	N.A.	NHL, HL	Etoposide (1.6 g/m^2 + G-CSF).	No	50%	N.A.	Cyclophoshamide + G-CSF (1) DHAP + G-CSF (5) ICE + G-CSF (6)	0
Junghanss et al. [32]	8	49.5 (28-62)	NHl, HL, GCT,	Etoposide 1.5-2 g/m^2 + G-CSF)	No	75%	75%	DexaBEAM (6) Taxotere/doxorubicin (1) EMACO (1), G-CSF alone (4)	0
Reiser at al. [28]	16	40 (22-68)	NHL, HL	Etoposide 2 g/m^2 + G-CSF	No	100%	81%	Cyclophosphamide 4 g/m^2 + G-CSF	0
Calderon-Cabrera et al. [29]	33	48 (37-67)	NHL, HL	Cytarabine 400 mg/m^2 i.v. days 1-3 + G-CSF	No	96.8%	93%	17 patients chemo + G-CSF, 16 patients G-CSF only	1
Koyama et al. [26]	6	49.5 (41-67)	NHL, HL	Etoposide 100 mg/m^2 i.v. + cytarabine 100 mg/m^2 i.v. days 1-4	No	83%	N.A.	5/6 Chemo + G-CSF, 1/6 G-CSF only	0
Kanfer et al. [27]	7	N.A.	MM, NHL, HL, ALL, AML, GCT.	Etoposide (2-1.8-1.6 g/m^2) + G-CSF	No	71%	N.A.	Cyclophosphamide (2-4 g/m^2) + G-CSF	0
Kanate et al. [31]	6	57	NHL, HL	Bone marrow harvest	No	16.67%	50%	G-CSF + plerixafor (6/6) 1/6 chemomobilization	6/6
Haverkos et al. [30]	6	55	NHL, HL	Etoposide 2 g/m^2 + G-CSF + plerixafor (3) Cyclophosphamide 3 g/m^2 + G-CSF + plerixafor (3)	Yes	100%	100%	G-CSF + plerixafor (6/6), 1/6 chemomobilization	6/6

AML indicates acute myeloid leukemia; ALL, acute lymphoid leukemia; GCT, germ cell tumor.

efficacy rate of almost 97% and limited toxicity. However, the cohort included only younger lymphoma patients (median age, 48 years), half of the patients had been previously mobilized with G-CSF only, and only 1 plerixafor failure was included, compared with 7 in our group. Junghanns et al. [32] reported results of 8 patients who had failed 1 or 2 mobilization attempts, with 6 (75%) reaching the target $CD34^+$ yields and proceeding to ASCT after salvage VP-16 (1.5 to 2 g/m^2) + G-CSF remobilization regimen. Grade 3 mucositis was reported in all cases, whereas 4 patients developed grades 3 and 4 infections, with 1 patient requiring admission to the intensive care unit. A few mostly first-line mobilization studies also included small numbers of mobilization failures. Kanfer et al. [27] reported 7 cyclophosphamide + G-CSF failures, who underwent salvage remobilization using VP-16 (1.6 to 2 g/m^2) + G-CSF. Five patients achieved >2 million $CD34^+$/kg, resulting in 72% efficacy. However, the authors did not report whether all 5 proceeded to ASCT [27]. Recently, Koyama et al. [26] presented a mobilization regimen Etoposide + Cytarabine consisting of VP-16 100 mg/m^2 + cytarabine 100 mg/m^2 on days 1 to 4 + G-CSF that was effective in 5 of 6 chemomobilization failures. No plerixafor failures were included in the study.

Only a few reports have been published on plerixafor failures (Table 6). Haverkos et al. [30] reported 6 successful cases of salvage chemomobilization combined with plerixafor after previous failed G-CSF + plerixafor mobilization attempts. Three patients received a salvage mobilization regimen of cyclophosphamide 3 g/m^2 + plerixafor and 3 were remobilized with VP-16 2 g/m^2 + plerixafor. All 6 patients proceeded to ASCT. However, only 1 patient had previously failed a chemotherapy-based PBSC mobilization. Another study reported an unsuccessful salvage mobilization strategy harvesting stem cells from the bone marrow in 6 patients who previously had failed a PBSC mobilization attempt using plerixafor + G-CSF [31].

To our knowledge, our study presents 1 of the largest groups of chemotherapy-based PBSC mobilization failures and shows that VP-16 2 g/m^2 + G-CSF 10 μg/kg/day with optional plerixafor is a highly effective regimen in these poor mobilizers. The regimen was also effective in all 7 patients who had earlier undergone unsuccessful plerixafor-based mobilizations, with only 1 patient requiring additional plerixafor.

The optimal dose of VP-16 is a matter of discussion. Because of prolonged myelosuppression after VP-16 the number of adverse events was relatively high, with febrile neutropenia and mucositis the most common. Several other studies also demonstrated substantial toxicities when VP-16 was used for first-line PBSC mobilization in high doses (1.5 to 2 g/m^2) [12,27]. In contrast, Mahindra et al. [14] demonstrated a lower toxicity profile (only 27% of readmissions with febrile neutropenia) in a much larger sample of patients who received first-line mobilization with VP-16 2 g/m^2, and no increased risk of therapy-related myelodysplasia or acute myeloid leukemia when compared with G-CSF–only mobilized patients was reported. Low rates of febrile neutropenia (7.6%) after high-dose VP-16 (1.6 g/m^2) were reported by Ozkan et al. [9]. Several authors have reported that administration of VP-16 at lower doses (600 mg/m^2 or 750 mg/m^2) resulted in successful frontline PBSC mobilization with a lower adverse event profile [10,11,13]. However, all patients in our cohort were very poor mobilizers who already had received 1 or 2 unsuccessful chemomobilization regimens. A significant dose reduction of VP-16 may also reduce efficacy because larger numbers of chemotherapy cycles were associated with poor mobilization [33,34]. Although controversial, the high dose of VP-16 may also result in higher reduction of residual malignant cells and better tumor control [35]. To reduce toxicity, we have decided to reduce the total dose of etoposide by 25% to 1.5 g/m^2 (375 mg/m^2, days 1 to 4) in our center. A follow-up analysis is needed to evaluate any changes in both toxicity and efficacy.

In conclusion, VP-16 + G-CSF ± plerixafor is an effective salvage stem cell mobilization regimen in patients regardless of previous plerixafor. The optimal VP-16 dose needs further studies.

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