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Application of First-Line Steady-State Mobilization *vs.* Conventional Chemotherapy Mobilization for Peripheral Hematopoietic Stem Cell Mobilization in Newly Diagnosed Multiple Myeloma Patients

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Abstract

Background: Plerixafor plus G-CSF (PLE+G-CSF) has demonstrated superior mobilization efficacy when compared with Cyclophosphamide plus G-CSF (CY+G-CSF) in Multiple Myeloma (MM) patients. However, the cost of plerixafor is relatively high in China. We aimed to explore a more efficient and economical mobilization scheme of HSC mobilization.

Methods: Outcomes of 95 patients with MM mobilized using P+G-CSF (n=47) or CY+G-CSF (n=48) before ASCT in our center were retrospectively analyzed. Only one preparation of plerixafor (sufficient dose in the first injection and the remaining in the second injection) was used in our center for steady-state mobilization. The mobilization efficiency, adverse reactions, average total cost of mobilization, and hematopoietic reconstruction after transplantation were analyzed and compared.

Results: The plerixafor mobilization strategy increased the success rate of mobilization (87.2% *vs.* 70.8%, P=0.050) and reduced the times of apheresis ((1 (1, 2) d *vs.* 2 (1, 3) d, P<0.001) compared with the CY+G-CSF group. There was no significant difference in the time of hematopoietic reconstruction between the two groups. PLE+G-CSF was associated with higher financial burden as high cost of plerixafor ($12,227.6 *vs.* $3,545.7, P<0.001), but lower rate of hospitalization, reduced need for salvage mobilization and antibiotics uses.

Conclusion: Our findings showed that even with one vial of plerixafor used for the whole mobilization process, PLE+G-CSF strategy, partially relieving the economic burden, had a higher success rate, fewer apheresis times, and lower adverse reactions than the CY+CSF strategy.

Keywords: Multiple myeloma; Hematopoietic stem cell mobilization; Autologous hematopoietic cell transplantation; Cyclophosphamide; Granulocyte colony-stimulating factor

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Introduction

The development of novel drugs over the last 20 years has changed the treatment landscape and clinical outcome of patients with Multiple Myeloma (MM), which significantly improves the Progression-Free Survival (PFS) of patients [1-3]. However, high-dose chemotherapy combined Autologous Stem Cell Transplantation (ASCT) is still considered the standard treatment for transplant-ineligible patients with Newly Diagnosed Multiple Myeloma (NDMM) [4,5]. Large-scale clinical studies have already demonstrated that ASCT could further improve the PFS of patients by almost 20 months [6,7]. According to the data from the Chinese Blood and Marrow Transplantation Registry (CBMTR), over the past 3 years, an increasing number of Chinese MM patients have been treated by ASCT, rising from the 27% in 2015 [8] to 41% in 2019 [9]. Mobilization and collection of enough Hematopoietic Stem Cells (HSC) are essential to ensure rapid and durable hematopoietic recovery after transplantation [10-12]. Thus, developing a high-quality mobilization scheme has become a major research concern.

Plerixafor (PLE), a small molecule CXC Chemokine Receptor 4 (CXCR4) antagonist, in combination with Granulocyte Colony-Stimulating Factor (G-CSF) has shown superior mobilization outcomes in comparison to G-CSF alone [13] and traditional chemotherapy mobilization, represented by high-dose Cyclophosphamide (CY)+G-CSF [14]. In addition, PLE+G-CSF can also avoid unnecessary exposure to the adverse effects of chemotherapy [15,16]. Nonetheless, its high costs limit general use. Chemotherapy mobilization is still the main mobilization strategy used for most Chinese patients with MM.

This study retrospectively analyzed the efficacy and safety of first-line mobilization with PLE+G-CSF, as well as engraftment in patients with MM treated in our center, whose data were compared with previous data of chemotherapy mobilization. The aim of the present study was to explore how to mobilize HSC with plerixafor more economically and efficiently.

Method

Patients and data collection

This retrospective study complies with the ethical standards of the institution, and performed in line with the principles of Helsinki Declaration. Approval was granted by the Ethics Committee of Zhejiang University College of Medicine First Affiliated Hospital. This is a retrospective study. The Research Ethics Committee has confirmed that no ethical approval is required.

Data of 47 MM patients who underwent first-line mobilization by plerixafor plus G-CSF (PLE+G-CSF group) in Bone Marrow Transplantation Center, Zhejiang University College of Medicine First Affiliated Hospital between April 2020 and November 2021 were retrospectively analyzed and compared with the retrospective historical control arm consisting of 48 MM patients who underwent chemotherapy mobilization by cyclophosphamide plus G-CSF (CY+G-CSF group) between November 2016 and July 2021. The inclusion criteria were as follows: 1) patients with newly diagnosed symptomatic MM who were eligible for ASCT; 2) those who underwent first-line mobilization by CY+G-CSF or PLE+G-CSF and underwent at least one apheresis. Exclusion criteria were: 1) complicated with lymphoma or other solid tumors; (2) MM patients who were previously mobilized or used other mobilization regimens; (3) those with one completed ASCT.

The following baseline characteristics of patients were collected: Age at mobilization, sex, weight, Durie-Salmon stage (DS stage) and International Staging System (ISS), induction therapies and disease status at mobilization.

Mobilization strategies

After the plerixafor (Mozobil) was approved in China, the choice of mobilization regimen was primarily based on physician preference; however, it was also driven by insurance constraints to a large extent since all third-party payers had yet to accept the upfront use of plerixafor for stem cell mobilization.

A recent literature reported that residual plerixafor after initial opening remained chemically stable for at least 2 weeks both at room temperature and under refrigeration [17], we recommend that patients try to use only one vial of plerixafor's mobilization scheme, as follows: G-CSF (10 ug/kg/d) was continuously injected subcutaneously from Day 1 to the harvest of stem cells was completed. On Day 4, if Peripheral Blood CD34+ cells (PBCD34+) count was <20 cells/μl, plerixafor (0.24 mg/kg or fixed dose of 20 mg, the choice of the specific dose was decided by the physician based on clinical experience; if Creatinine Clearance Rate (CCR) ≤ 50 ml/min, the dose was reduced by one third to 0.16 mg/kg) was given at 22:00, while the remaining plerixafor was labeled and stored at 4°C in a refrigerator. Apheresis started at 8:00 on the Day 5. If $<2 \times 10^6$ cells/kg CD34+ cells were harvested on first apheresis, the remaining plerixafor was injected subcutaneously at 22:00 on Day 5 night. The apheresis procedure repeated on the Day 6. If the total number of CD34+ cells collected twice still $<2 \times 10^6$ cells/kg, no more plerixafor was given on the Day 6 night and the apheresis carried out on the Day 7 only with G-CSF. Patients underwent no more than three apheresis in this study (Figure 1A).

For the patients in the CY+G-CSF group, it should be noted that before 2020, the monitoring of PBCD34+ had not been fully carried out in our center. Thus, the apheresis time of chemotherapy mobilization is mainly based on peripheral blood leukocyte count. CY with the total dose of 3 g/m^2 was intravenous infusion in two days. Then the count of White Blood Cells (WBC) was measured every day. G-CSF (10 ug/kg) was administered when WBC$<1.0 \times 10^9$/L and then apheresis was performed when WBC $>3.0 \times 10^9$/L. Patients underwent no more than three apheresis (Figure 1B).

All collections were performed with a COBE SPECTRA apheresis system (Terumo BCT. Inc. Lakewood, CO, USA). The BD FACSCanto™ II flow cytometer (BD Biosciences, San Jose, CA, USA) was used for all analyses. The final harvests were cryopreserved in 10% DMSO using a controlled rate freezer and preserved in liquid nitrogen. The minimum target aim was defined as CD34+ $\geq 2 \times 10^6$ cells/kg to meet the demand of at least one ASCT [11,12]. The high-quality mobilization target was defined as CD34+ $\geq 5 \times 10^6$ cells/kg [10].

Transplant procedure and supportive care

All patients underwent conditioning by the regimen of bortezomib combined with melphalan (bortezomib: Subcutaneous injection of 1 mg/m^2, -6 d, -3 d, +1 d, and +4 d; melphalan: Intravenous infusion, 200 mg/m^2, -2 d); melphalan only, if the patient had accompanying neurological disorders. If CCR was <60 ml/min, the melphalan dose was reduced to 140 mg/m^2 [18]. Infusion of autologous PBSCs was performed on day 0. All patients received growth factor support, blood products support, fungal, herpes and bacterial prophylaxis per institutional guidelines.

Criteria for hematopoietic reconstitution were as follows: ANC $>0.5 \times 10^9$/L for 3 continuous days after G-CSF treatment was stopped considered as meeting the criteria of granulocyte reconstitution; PLT maintained $>20 \times 10^9$/L for 7 continuous days after platelet infusion stopped was considered as meeting the criteria of megakaryocytes. Delayed hematopoietic reconstitution referred to failing to meet either of the criteria after 28 days.

Complications

Adverse reactions to the two mobilization strategies were collected by reviewing the medical records and laboratory examination results. The adverse reactions were classified according to the CTCAE5.0 criteria.

Cost determination

Data on costs of patients all came from the summary list of the hospital case system. All expenses are pre-reimbursed by health insurance. Cost analysis included the following aspects: pre-apheresis

session (including hospitalization days for CY/PLE administration, CVC positioning and cost of mobilizing agents and antibiotic treatment due to febrile neutropenia until discharge from hospital); peri-apheresis session (including apheresis session, CD34+ counts, blood counts, biochemical parameters (creatinine, electrolytes blood test); and post-apheresis session (including storage cost). Medication prices were based on the price of centralized procurement of drugs in China. Costs are shown in Table 1 and are adjusted to reflect 2021 US dollars.

Statistical analysis

The Chi-square test or Fisher exact test was performed for the comparison of categorical variables. Shapiro-Wilk test was performed to test for normality of continuous data. Quantitative data with normal distribution were expressed as means ± SD (Standard Deviation), and quantitative data with non-normal distribution were described by median (P25, P95). For the comparison of continuous data, a t-test was used for data with normal distribution, and the Mann-Whitney U test for data with non-normal distribution. SPSS 26.0 software was used for descriptive statistics. A P value <0.05 was considered statistically significant.

Results

Patients' baseline and treatment characteristics

Table 2 shows the baseline characteristics of the 95 MM patients who underwent HSC mobilization, among whom 47 were in the PLE+G-CSF group and 48 were in the CY+G-CSF group. Besides age, DS stage, and induction therapy before mobilization, other baseline characteristics did not significantly differ between the two groups. Patients in PLE+G-CSF group although on average older, had lower disease severity according to DS stage. The successive use of CY+G-CSF and PLE+G-CSF implies that most patients in the former had never received Daratumumab or Lenalidomide which were becoming standard therapies during treatment of the latter group. The MRD negative rate before mobilization was 34/46 (73.9%; 1 missing) in the group *vs.* 14/38 (36.8%; 10 missing) in the PLE+G-CSF and CY+G-CSF groups, respectively (P<0.001).

Table 1: Costs of mobilization procedure and medication.

Treatment component	Unit-price[a,b] (US dollars, 2021)
Pre-apheresis session	
CVC positioning	92.5
Blood counts	3.1
Biochemical parameters	13.8
G-CSF (filgrastim)/150 ug/0.9 ml s.c.	10.9
Treatment-specific costs	
Plerixafor/24 mg/1.2 ml s.c.	10153.2
CY/0.3 g iv.gtt.	3.7
Mesna/0.4 g/2.4 ml iv.gtt.	1.4
Palonosetron hydrochloride/0.25 mg/5 ml iv.gtt.	15.4
Hydration alkalization iv.gtt.	9.2
Cost of apheresis	
Apheresis session	682
Cryopreservation (First time)	232.5
CD34+flow cytometry	15.5
CD34+immunohistochemistry	77.5
Others[c]	69.8
Hospitalization costs/day[d]	12.1

[a]The drugs costs were calculated according to the price of centralized procurement of drugs (excluding plerixafor), and were before Chinese Medicare reimbursement. [b]These fees did not include the cost of intravenous drip and subcutaneous injection. [c]Including hematopoietic stem cell culture identification and T cell subset analysis. [d]Hospitalization costs only included daily bed fee, nursing fee and the medical check-up fee.

Table 2: Patient Characteristics.

Characteristics	Mobilization strategy		*P* value
	PLE+G-CSF (N=47)	CY+G-CSF (N=48)	
Weight, kg (P25, P75)	65 (56.72)	63 (55.70)	0.423
Median age, years (P25, P75)	58 (52.61)	53 (47.58)	0.009
Male, N (%)	28 (59.6%)	22 (45.8%)	0.180
Durie-Salmon stage, N (%)			0.013
I	4 (9.3%)	0	
II	9 (20.9%)	3 (6.3%)	
III	30 (69.8%)	42 (87.5%)	
Missing	4 (8.5%)	3 (6.3%)	
International staging system, N (%)			0.483
I	12 (25.5%)	16 (33.3%)	
II	13 (27.7%)	10 (20.8%)	
III	15 (31.9%)	11 (22.9%)	
Missing	7 (14.9%)	11 (22.9%)	
Prior treatment, N (%)			
Lenalidomide	32 (68.1%)	19 (39.6%)	0.005
Daratumumab	7 (14.9%)	0	0.017
Disease status premobilization, N (%)			0.169
PR	1 (2.1%)	6 (12.5%)	
VGPR	24 (51.1%)	24 (50.0%)	
(s)CR	22 (46.8%)	18 (37.5%)	
MRD negative, N (%) [a]	33 (70.2%)	14 (36.8%)	<0. 001

[a]Data were missing for 10 (20.8%) patients in the CY+G-CSF group and 1 (2.1%) patient in the PLE+G group.
PLE: Plerixafor; CY: Cyclophosphamide; MRD: Minimal Residual Disease

Stem cell harvest efficiency

The data of stem cell mobilization and harvest are shown in Table 3. The plerixafor administration group required less apheresis days to reach the target CD34+ number (P=0.039). Although the median number of CD34+ cells in the PLE+G-CSF group was higher [4.6 (3.2, 6.0) × 10^6 cells/kg] than in the CY+G-CSF group [3.9 (1.5, 7.7) × 10^6 cells/kg], the impression of higher harvest and mobilization in PLE+G-CSF group was not confirmed by statistical analysis (P=0.824). Twelve (25.5%) patients in the PLE+G-CSF group and 35 (72.9%) in the CY+G-CSF group failed to yield the desired minimum of 2 × 10^6 CD34+ cells per kg on the first apheresis day (P<0.001) and all of them, but one in the PLE+G-CSF group, performed a second apheresis session. Finally, six (12.8%) patients in the PLE cohort failed to mobilize versus 14 (29.2%) in the CY cohort. They all preceded a second mobilization attempt, except one and two patients in the PLE and CY+G-CSF group, respectively. Unfortunately, there were still two patients failed a second mobilization attempt and could not undergo ASCT.

Seventeen (36.2%) patients in the PLE+G-CSF group received fixed-dose (20 mg) mobilization (FD group), and 27 patients (57.4%)

Table 3: Stem cell harvest efficiency.

	Mobilization strategies		P value
	PLE+G-CSF (N=47)	CY+G-CSF (N=48)	
Total number of CD34+cells collected, × 10^6/kg, median (P25, P95)	4.58 (3.17, 5.99)	3.90 (1.45, 7.74)	0. 824
Successful mobilization (≥ 2 × 10^6/kg), N (%)	41 (87.2%)	34 (70.8%)	0.05
Successful mobilization on day 1(≥ 2 × 10^6/kg), N (%)	35 (74.5%)	13 (27.1%)	<0.001
High-quality mobilization (≥ 5 × 10^6/kg), N (%)	18 (38.3%)	19 (39.6%)	0.898
High-quality mobilization on day 1(≥ 2 × 10^6/kg), N (%)	6 (12.5%)	11 (23.4%)	0.166
Days of apheresis required for successful mobilization, median (P25, P95)	1 (1, 2)	2 (1, 3)	<0.001
Days of apheresis required for high-quality mobilization, median (P25, P95)	1 (1, 2)	2 (1, 2)	0.039

PLE: Plerixafor; CY: Cyclophosphamide; MRD: Minimal Residual Disease

Table 4: Patients in PLE+G-CSF group requiring second apheresis.

No. of patients	Sex	Weight, kg	Number of apheresis session	First given plerixa for dose, mg	First given plerixa for dose, mg/kg	Remaining plerixa for dose, mg	Remaining plerixafor BW, mg/kg	PBCD34+ at Baseline, /μl
1	Male	58	2	20	0.34	4	0.07	Miss
4	Male	66	3	20	0.3	4	0.06	Miss
7	Female	62	2	20	0.32	4	0.06	Miss
8	Male	70	2	20	0.29	4	0.06	13
10	Male	83	2	20	0.24	4	0.05	4
14	Male	61	2	20	0.33	4	0.07	Miss
15	Female	57	3	20	0.35	4	0.07	3
17	Female	60	3	20	0.33	4	0.07	2
18	Female	49	2	12	0.24	12	0.24	4
19	Male	70	2	12	0.16	12	0.17	9
20	Female	53	2	13	0.24	11	0.21	1
22	Male	79	2	13	0.16	11	0.14	11
23	Male	53	2	13	0.24	11	0.21	2
26	Male	81	2	24	0.3	0	0	9
28	Male	75	2	18	0.24	6	0.08	Miss
29	Male	75	2	18	0.24	6	0.08	5
30	Male	55	2	14	0.24	10	0.17	7
31	Male	62	2	15	0.24	9	0.15	3
32	Male	65	2	16	0.24	8	0.12	11
34	Male	73	2	24	0.33	0	0	13
36	Male	66	2	11	0.16	13	0.2	5
37	Male	65	2	16	0.24	8	0.12	3
38	Female	54	2	13	0.24	11	0.2	7
40	Female	60	3	15	0.24	9	0.15	1
41	Female	36	2	12	0.33	12	0.33	2
43	Male	65	2	16	0.24	8	0.12	1
44	Male	65	2	16	0.24	8	0.12	8
45	Female	73	3	17	0.24	7	0.1	4
47	Male	85	2	24	0.28	0	0	10

PBCD34+ peripheral blood CD34+ cells

were mobilized by weight-based doses (0.24 mg/kg) (WB group) (except for three people who used complete dosages, 24 mg). The successful mobilization rate (94.1% *vs.* 81.5%, P=0.460) and the mean number of CD34+ cells collected (4.6 ± 1.9 × 10^6 cells/kg *vs.* 4.5 ± 2.2 × 10^6 cells/kg, P=0.925) between the FD group and WB group were not significantly different. Twenty-nine (61.7%) patients in the PLE+G-CSF group underwent ≥ 2 apheresis sessions, eight and 18 patients in FD group and WB group, respectively (Table 4). No statistically significant effects on PBCD34+ (29.8 ± 17.4 cells/μl *vs.* 31.5 ± 20.0 × 10^6 cells/μl, P=0.763) and CD34+ cells (2.2 ± 1.1 × 10^6 cells/kg *vs.* 2.0 ± 1.2 × 10^6 cells/kg, P=0.532) were observed on the first and second apheresis day. Although the patients received only 4 mg

Table 5: Advent events.

Adverse Events	Total		P value	Grade 3-4		P value
	PLE +G-CSF(N=47)	CY+G-CSF(N=48)		PLE +G-CSF(N=47)	CY+G-CSF (N=48)	
Hematological toxicity, N (%)						
Febrile neutropenia	0.00%	22 (45.8%)	<0.001	0	17 (35.4%)	<0.001
Anemia	18 (38.3%)	40 (83.3%)	<0.001	1 (2.1%)	7 (14.6%)	0.029
Thrombocytopenia	2 (4.3%)	33 (68.8%)	<0.001	0	6 (12.5%)	0.037
Non-hematologic toxicity, N (%)						
Nausea	5 (10.6%)	15 (31.3%)	0.014	0	0	-
Vomiting	3 (6.4%)	12 (25.0%)	0.013	0	0	-
Diarrhea	16 (34.0%)	10 (18. 8%)	0.149	3 (6.4%)	2 (4.2%)	0.981

PLE: Plerixafor; CY: Cyclophosphamide

Table 6: Mobilization costs [a].

	Mobilization strategies		P value
	PLE+G-CSF (N=47)	CY+G-CSF (N=48)	
Average hospitalization cost (median)	76.9 (72.5)	194.5 (193.5)	<0.001
Average treatment-specific cost (median)	10189.8 (10184.2)	176.2 (177.0)	<0.001
Average G-CSF cost (median)	267.6 (253.2)	335.3 (312.5)	0.001
Average total mobilization costs (median)	12227.6 (11798.8)	3545.7 (3371.3)	<0.001
Average antibiotics cost	26.7	187.2	<0.001
Average mobilization cost of patients of first apheresis (median)	11673.0 (1167.3)	1882.6 (1877.7)	<0.001
Average mobilization cost only on second apheresis day	1154.7	1138.8	<0.001
Average mobilization cost only on second apheresis day if standard plerixafor dose	11307.8	1138.8	<0.001

[a]Costs are shown in Table 1 and are adjusted to reflect 2021 US dollars.
PLE: Plerixafor; CY: Cyclophosphamide

(mean 0.06 mg per kg body weight) dose of plerixafor for the second apheresis in the FD group, no statistical difference in the number of CD34+ cells collected were observed ($1.8 \pm 0.8 \times 10^6$ cells/kg *vs.* $1.8 \pm 1.0 \times 10^6$ cells/kg, P=0.809), too.

Complications

Table 5 shows the main treatment-related adverse reactions including hematological toxicity and gastrointestinal reactions in two groups. Compared with the PLE+G-CSF group, the incidence and severity of hematological toxicity were significantly higher in the CY+G-CSF group. In the CY+G-CSF group, two patients need platelet and red blood cell transfusion requirement (One infused 11 platelet units, another infused three RBC units and 12 platelet units); however, none in PLE group. Antibiotics are also used more frequently in chemo-mobilization group (45.8% *vs.* 14.9%, P=0.001), increasing some of the hospitalization. The main adverse gastrointestinal response in plerixafor group was diarrhea, which occurred in a condition similar to the chemotherapy group.

The above symptoms could be improved after symptomatic treatment and quickly recovered after mobilization. No one in the two groups discontinued mobilization due to an adverse event.

Mobilization costs

Mobilization costs are summarized in Table 6. The total costs of mobilizing in the PLE+G-CSF group was much higher than in the chemotherapy group, largely due to the high price of plerixafor ($12,227.6 *vs.* $3,545.7, respectively; P<0.001). For those who need to receive a second apheresis session, the costs have gone up nine-fold if in accordance with the standard scheme of plerixafor. However, the administration of plerixafor was associated with significantly less costs for hospitalization (P<0.001), G-CSF (P=0.0001), and antibiotics administration (P<0.001).

Transplant and post-transplant outcomes

In our study, patients in the PLE+G-CSF group received mobilization between April 2020 and November 2021. As of the follow-up deadline (December 31, 2021), not all patients in the group have received ASCT, which resulted in a difference in the transplantation rate between the two groups: 33 patients (70.2%) in the PLE+G-CSF group *vs.* 43 patients (89.6%) in the chemotherapy mobilization group (P=0.018). One patient failed the implant post-transplant and died in the CY+G-CSF group. The median time of neutrophil engraftment was 11 (11, 12) days in the PLE+G-CSF group and 12 (11, 12) days in the CY+G-CSF group (P=0.184); the median time of platelet engraftment was 13 (12, 16) and 12 (11, 14) days, respectively (P=0.131).

Discussion

The price of plerixafor is expensive ($10,153.2) in China. Compared with chemotherapy mobilization, plerixafor alone create a greater financial burden for patients. Therefore, our center explored the feasibility of mobilization with plerixafor by only one vial. The findings of this study demonstrated that plerixafor-treated mobilization increased success rate of mobilization, reduced the times of apheresis, and substantially decreased the incidence of adverse reactions compared with the patients in CY+G-CSF group [15,19,20]. The dose-adjusted plerixafor-given regimen could be well tolerated by MM patients and in agreement with a host of other reports [21,22]. A single-center study in Mexico investigated the efficacy of half-dose plerixafor (0.12 mg/kg) +G-CSF (10 μg/kg) for the mobilization in 20

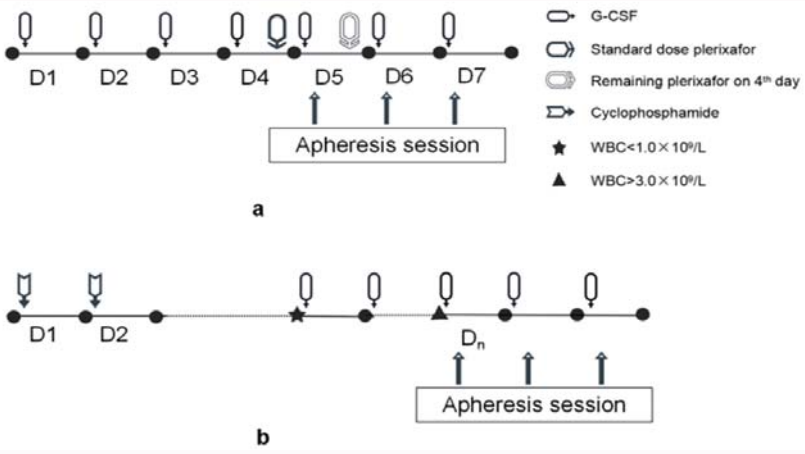

Figure 1: Mobilization Strategies. A) G-CSF was continuously used until the harvest of stem cells was completed. Standard dose plerixafor (0.24 mg/kg or fixed dose of 20 mg) was subcutaneously injected at 22:00 on the Day 4. The stem cells were harvested at 8:00 on the Day 5. If insufficient stem cells were harvested (<2 × 10^6 cells/kg), the remaining plerixafor was given at 22:00 on the Day 5 (24 mg minus the dose of the first injection on Day 4), and the apheresis procedure repeated on the Day 6. If the total number of CD34+ cells collected twice still <2 × 10^6 cells/kg, no more plerixafor was given on the Day 6 night and the apheresis carried out on the Day 7 only with G-CSF. B) Cyclophosphamide with the total dose of 3 g/m^2 was intravenous infusion in two days. G-CSF was administered for mobilization when WBC counts were <1.0 × 10^9/L. Apheresis was performed when WBC count >3.0 × 10^9/L. All patients underwent no more than 3 harvests.

MM patients and lymphoma patients. One apheresis procedure was sufficient to obtain at least 2 × 10^6 CD34+ cells/kg in 85% of patients [21]. Sanikommu et al. investigated the mobilization effects of fixed-dose plerixafor (12 mg) +G-CSF (10 μg/kg) in 19 patients with plasma cell tumors and lymphoma, revealing that compared with the standard dose (0.24 mg/kg), the spilt dosing was as effective but less expensive than standard dosing [22].

Economic analysis was also carried out in this study. In contrast to past research results that CY+G-CSF was associated with higher financial burden ($72,138 *vs.* $52,200, P=0.001) [14,23], or mobilization costs are offset by side effects of chemotherapy (like higher rate of hospitalization, increased need for salvage mobilization, and increased G-CSF use account) [19]. These costs difference due to chemotherapy toxicity was reflected in our study as well (Table 6), but the total costs of PLE+G-CSF group were significantly higher than that of CY+G-CSF group ($12,227.6 *vs.* $3,545.7, P<0.001), consistent with the analysis by Chaudhary et al. [15] largely because of the cost of this effective, but expensive, medication [15]. The average total cost of mobilization in Lebanon was also slightly higher in the plerixafor group ($7,886 *vs.* $7,536; P=0.16) [16]. However, for patients who need twice or more leukapheresis attempt in our study, the cost savings of the unused plerixafor are thus nearly 90%; that is, about more than 45% of the total mobilization cost. Therefore, for those who require multiple apheresis procedures, the dose-adjusted plerixafor-mobilization regimen in our center can reduce the financial burden to some extent, and is effective and feasible.

Consistent with a phase 4 clinical study performed in lymphoma patients after the marketing of plerixafor, although the fixed dose of 20 mg was higher than the body weight-specific dose in patients with low body weights, the mobilization efficiency was not significantly different [24]. However, in our study, the remaining dose (4 mg) of plerixafor is too small for patients who use a fixed dose of 20 mg. While there was no difference in the number of CD34+ cells collected on two apheresis days for the eight patients in the FD group (P=0.809), the effect of G-SCF could not be ignored. And no difference in the number of stem cell cells collected twice in the WB group (P=0.532). Researches in healthy human volunteers indicated that at doses above 0.16 mg/kg, plerixafor may be clinically useful for mobilization of progenitor cells for hematopoietic transplantation [25,26], the 0.24 mg/kg doses of plerixafor were well performed and tolerated in patients with MM and NHL [27]. However, dose-finding studies in combination with G-CSF were never performed to our knowledge. Research shows when healthy people are given G-CSF for 10 days the number of PBCD34+ begins to increase on the fourth day, reaches a maximum on the sixth day and then decreases [28]. Therefore, we speculate that for the patient's required second apheresis (sixth day of use of G-CSF), lower-than-standard plerixafor doses are also feasible.

A report on nutrition and chronic diseases of Chinese residents released in 2020 shows that the average body weight of men and women aged 18 and above in China is 69.6 kg and 59 kg, respectively [29], which means 7.3 mg to 9.8 mg (0.10 mg to 0.16 mg per kg body weight) dose of plerixafor will be left. Therefore, we recommended using the weight-based dose for mobilization in the modified plerixafor mobilization strategy, as a higher dose of plerixafor could be left for the injection on the second day.

However, the present study has some limitations. As a single-center retrospective study with a small sample size, the research results should be compared with the standard scheme, so as to prove the feasibility of adjusting the dose scheme more reliably. Then, a large proportion of patients were unable to obtain the data of PBCD34+ counts, especially in the chemo-mobilization group. Therefore, it was difficult to judge whether the two groups have a similar risk of mobilization failure at baseline. One thing that has to be mentioned is that the mobilization failure rate in our study (12.8%) was higher in comparison to previous reported studies (2% to 6%) [15,23,30,31], it may be related to the no full-dosage plerixafor scheme. Therefore, for more rational and effective application of plerixafor, the followed study could explore a personalize risk stratification to identify patients who need to receive full-dose daily treatment.

Conclusion

In summary, steady-state mobilization though plerixafor is, the costs are much higher than that of chemotherapy mobilization. Our exploratory study suggests that further study of plerixafor dosing in

combination with G-CSF and with consideration of cost would be necessary. Only one vial preparation of plerixafor may also be an effective mobilization for patients with MM, which can also result in successful CD34+ cell, but further reduce the financial burden of Chinese patients, improve patients' mobilization experience.

Clinical practice points

- High-dose chemotherapy combined autologous stem cell transplantation is the standard treatment for transplant-ineligible patients with newly diagnosed multiple myeloma. Plerixafor plus G-CSF has shown superior mobilization outcomes and can also avoid unnecessary exposure to the adverse effects of chemotherapy mobilization. Nonetheless, its high costs limit general use.

- Even with one vial of plerixafor used for the whole mobilization process, PLE+G-CSF strategy had a higher success rate, fewer apheresis times, and lower adverse reactions than the CY+CSF strategy, which partially relieved the economic burden.

- It is necessary to consider the cost of plerixafor in clinical practice. For more rational and effective application of plerixafor, a further study aimed to explore a personalize risk stratification to identify patients who need to receive full-dose daily treatment is needed.

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