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High-dose Versus Low-dose Cyclophosphamide in Combination with G-CSF for Peripheral Blood Progenitor Cell Mobilization

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Background : To compare the mobilizing effects and toxicities of two different doses of cyclophosphamide (CY) plus lenograstim (glycosylated G-CSF), we performed a prospective randomized study by enrolling patients suffering with either high-risk Non-Hodgkin's lymphoma (NHL) or breast cancer undergoing ablative chemotherapy.

Methods : The NHL patients received 4 cycles of CHOP and the breast cancer patients received 2-3 cycles of FAC (FEC) adjuvant chemotherapy. Then, the patients were randomly allocated to receive CY 4 g/m^2 (arm A) or 1.5 g/m^2 (arm B) in combination with lenograstim. Large volume leukapheresis was carried out and it was continued daily until the target cell dose of 2×10^6 CD34+ cell/kg was reached.

Results : Twenty-seven patients were enrolled in the study. The median number of leukaphereis sessions actually performed was 2.5 sessions in arm A and 3 sessions in arm B. The target cell dose was obtained with the median number of one leukapheresis session in both arms of the study (p=0.09). The collected number of CD34+ cells in the leukapheresis products was higher in arm A than arm B (22.4 vs. 9.9×10^6/kg, respectively, p=0.05). Grade III or IV leukopenia was present in 14/15 patients (94%) in arm A and in 1/12 patients (8%) in arm B (p<0.0001). Grade III or IV thrombocytopenia was present in 8/15 patients (54%) in arm A, but this was not present in any patients of arm B (p=0.0004). Neutropenic fever occurred in 6/15 patients (40%) in arm A, and in 1/12 patients (8%) in arm B (p=0.09). The hematological recovery of the leukocytes and platelets after transplantation was not statistically different between the two doses.

Conclusion : Low-dose CY plus lenograstim is a safe and effective mobilizing regimen.

Key Words : Cyclophosphamide; Hematopoietic stem cell mobilization; Progenitor cell; Granulocyte colony-stimulating factor

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INTRODUCTION

Mobilized peripheral blood progenitor cells (PBPC) have replaced the bone marrow as the source of stem cells for autologous stem cell transplantation (SCT)[1]. Chemotherapy and hematopoietic growth factor (HGF), either alone or in combination, increases the number of circulating progenitor cells. A few randomized trials that have compared mobilization approaches have been reported on[2-5], but a variety of methods has been shown to effectively increase the PBPC yield while decreasing the number of required apheresis procedures. There are numerous studies that have strongly suggested that the addition of HGF, such as G-CSF and GM-CSF, to the myelosuppressive chemotherapy enhances the mobilization while it reduces the myelotoxicity[6, 7]. A combination of chemotherapy and HGF is currently the most frequently used protocol[8].

Many different myelosuppressive chemotherapy protocols have been used for mobilization in conjunction with HGF. Although the best protocol is not yet known, high-dose cyclophosphamide (CY) (3-7 g/m^2) is the most commonly reported protocol because it is active against most tumors and it can be justifiably given even for diseases when the conventional treatment is not sufficiently myelosuppressive[9]. However, the main limitations at this dosage of CY are neutropenic sepsis and bleeding even with the addition of HGF. Another emerging impression is that adequate mobilization with less morbidity may occur even with the chemotherapy regimen that is only mildly myelotoxic, such as CY at 1-2 g/m^2[2, 10, 11].

In this randomized trial, we evaluated the PBPC mobilizing effect of high-dose CY (4 g/m^2) versus low-dose CY (1.5 g/m^2) that was given in combination with lenograstim (glycosylated G-CSF). We compared the kinetics of the progenitor mobilization, the number of apheresis sessions that were required to obtain the target cell dose, the hematological recovery after SCT and the toxicities.

MATERIALS AND METHODS

Patient eligibility

Patients with high-risk non-Hodgkin's lymphoma (NHL) or high-risk breast cancer (BC) who were scheduled to undergo PBPC mobilization for autologous SCT were enrolled. The patients ranged in age from 16 to 60 years, and the patients with an Eastern Cooperative Oncology Group performance status of 0 to 2 were included in the study. High-risk NHL patients were defined as those who had a histologic subtype of diffuse mixed, diffuse large or immunoblastic lymphoma according to NCI Working Formulation, and they were placed in the high-intermediate or high risk group according to the age-adjusted International Prognostic Index. The patients had to have a complete or partial response to induction chemotherapy. High-risk BC patients were defined as those who had received radical mastectomy and had involvement of 10 or more axillary lymph nodes. Those patients who had inflammatory BC or who had received post-operative radiation therapy were excluded from the study. The study protocol was approved by the Institutional Review Board of each participating medical center, and all the patients gave us their written informed consent.

Mobilization of PBPC

The high-risk NHL patients received induction chemotherapy that consisted of 4 cycles of CHOP (CY 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; vincristine 1.4 mg/m^2 IV on day 1; prednisolone 100 mg/m^2 per oral on days 1 through 5). The high-risk BC patients received adjuvant chemotherapy with 2-3 cycles of FEC or FAC (5-fluorouracil 600 mg/m^2 IV on day 1; epirubicin 60 mg/m^2 or doxorubicin 50 mg/m^2 IV on day 1; CY 600 mg/m^2 IV on day 1). After this, the patients were randomized to either the A or B arms of the study. Randomization was done by the coordinating center, and the patients were stratified as NHL or BC. The patients who were randomized to arm A and arm B received CY 4 g/m^2 and 1.5 g/m^2 IV on day 1, respectively. Lenograstim (250 μg/day) was given subcutaneously at around 9 PM from the third day until the day before the final leukapheresis (Figure 1).

PBPC harvest and cryopreservation

Leukapheresis was begun when the WBC count reached

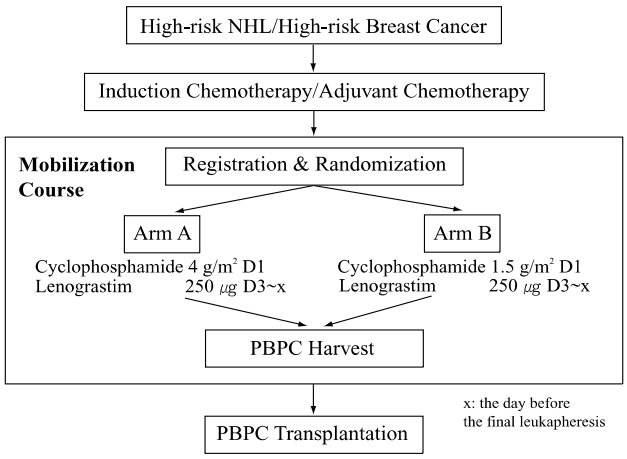

Figure 1. Schematic representation of the treatment protocol. Patients with high-risk non-Hodgkin's lymphoma or breast cancer who were eligible for autologous transplantation were randomized to receive high-dose (4 g/m^2) or low-dose (1.5 g/m^2) cyclophosphamide in combination with lenograstim after induction chemotherapy with CHOP for the NHL patients or adjuvant chemotherapy with FAC for the breast cancer patients.

above 3×10^9/L after the nadir, and it was continued daily until the target cell dose of 3×10^8 MNC/kg or 2×10^6 CD34+ cells/kg was reached. However, if the WBC count did not fall below 3×10^9/L, leukapheresis was commenced when the WBC count began to increase after the nadir. The PBPCs were harvested by large volume leukapheresis by processing approximately 3 blood volumes. All the collected samples were cryopreserved using 10% dimethylsulfoxide as a cryoprotectant, and the samples were stored in liquid nitrogen until further use.

Measurement of CD34+ cells and CFU-GM

To evaluate the PBPC kinetics, CD34+cell measurement and CFU-GM assay in the PB was done every other day from the first day of CY administration until the first leukapheresis, and then it was daily thereafter until the final leukapheresis. The measurements were also done in every apheresis product. All the samples from each participating center were transported to the Seoul National University Hospital in fresh state for the CD34+ cell measurement and the CFU-GM assay. CD34+ cell measurement was done by using a ProCOUNT kit (Becton Dickens, USA) and a CFU-GM assay by MethoCult H4531 (StemCell Technologies, USA).

High-dose chemotherapy and stem cell transplantation

The high-risk NHL patients received high-dose chemotherapy (HDC) with the BEAM protocol (BCNU 300 mg/m^2 IV on day 7; etoposide 200 mg/m^2/d IV on days 6 through 3; cytarabine 200 mg/m^2 IV on days 6 through 3; melphaln 140 mg/m^2 IV on day 1). The high-risk BC patients received HDC with the CBP protocol (BCNU 400 mg/m^2 IV on day 6; CY 2 g/m^2 IV on days 5 through 3, cisplatin 55 mg/m^2 IV on days 5 through 3). At 48 hours after the last dose of chemotherapy, the autologous PBPCs were rapidly thawed in a 37℃ water-bath and then they were infused via a central venous catheter without filtering. Lenograstim was administered until the recovery of the patients' marrow function.

Statistical analysis

This study was originally designed as an open, randomized, multi-center, parallel-group phase III trial for comparing the two doses of CY for their ability to mobilize PBPCs in combination with lenograstim. The primary endpoint of the study was the number of leukapheresis sessions that was required to obtain the target cell number. We assumed that the clinically significant difference between the two groups was 1 and the standard deviation was 1.2. The number of patients that needed to be recruited was estimated to be 20 in each arm with a significance level of 5 percent and a power of 80 percent when assuming a dropout rate of 15 percent. The secondary endpoints were the kinetics of the PBPCs' mobilization, the toxicity of the two different mobilization methods and the patients' hematological recovery after transplantation. The time to neutrophil and platelet engraftment were, respectively, defined as the number of days needed after the infusion of PBPC to achieve an ANC$\geq0.5\times10^9$/L and a platelet count$\geq20\times10^9$/L, and this was independent of platelet transfusions that were done for more than 3 consecutive days.

Descriptive statistics are presented as the median and the range, unless otherwise specified. The Mann-Whitney U test was used for analyzing the continuous variables. Comparison of the categorical variables was performed using Fisher's exact test or the chi-square test. The relationship between the different hematological parameters of the PB and the leukapheresis products was estimated by using non-parametric Spearman rank correlation. All the statistical tests were two-sided, and the differences were considered significant if the p values were <0.05.

RESULTS

Patient characteristics

The study was prematurely closed due to the poor patient accrual. Twenty-seven patients were enrolled and randomized between June 1999 and January 2002. Fifteen patients received high-dose CY (arm A), and 12 patients received low-dose CY (arm B) for the PBPCs' mobilization. The median age of the patients was 44.5 years (range: 19-58) in arm A and 40 years (range: 24-59) in arm B. The male-to-female ratio was 7:8 in arm A, and it was 5:7 in arm B. The number of patients with NHL versus BC was 7:8 in arm A and 6:6 in arm B. The patient characteristics in both arms of the study were not statistically different (Table 1).

Peripheral blood kinetics

The mean WBC count in the PB prior to the CY administration was 5.6×10^9/L (95% CI : $4.0\text{-}7.2\times10^9$/L) in arm A and it was 5.5×10^9/L (95% CI : $4.5\text{-}6.5\times10^9$/L) in arm B. In arm A, the WBC count reached the peak on day 4, it began to decline rapidly from day 6 and it reached the nadir on day 9 (nadir time range: 8-10). The mean WBC count at the nadir was 0.56×10^9/L (95% CI : $0.29\text{-}0.92\times10^9$/L). After then, it began to increase and it exceeded 3.0×10^9/L on day 11 (range: 9-14 days). In arm B, the WBC count increased rapidly from day 4, but it did not decrease abruptly after this time. The nadir was on day 9 (nadir time range: 6-11 days), and the mean WBC count at this time was 10.1×10^9/L (95% CI : $7.5\text{-}17.9\times10^9$/L).

The mean CD34+ cell count in the PB prior to CY administration was 15×10^6/L (95% CI : $4\text{-}26\times10^6$/L) in arm A

Table 1. Patient characteristics

	Arm A (n=15)	Arm B (n=12)	*p* value
Age, years			
Median (range)	44.5 (19-58)	40 (24-59)	0.7
Gender			
Male/female	7/8	5/7	0.9
Disease			
NHL	7	6	0.8
Breast cancer	8	6	
Stage at diagnosis			
NHL (I/II/III/IV)	1/1/2/3	0/0/1/5	0.4
Breast cancer (IIB/IIIA)	3/5	0/6	0.2
Bone marrow involvement			
n (%)	1 (7%)	1 (8%)	1.0

Table 2. Peripheral blood progenitor cell harvest parameters

	Arm A (n=15) median (range)	Arm B (n=12) median (range)	*p* value
Time to leukapheresis (days)	10 (9-13)	9 (7-11)	
Total number of leukapheresis sessions	2.5 (2-5)	3 (2-4)	0.02
Whole blood processed (liters)	49.3 (30-85)	48.7 (30-69)	0.3
Mononuclear cells ($\times 10^8$/kg)	(n=13)	(n=10)	0.8
CD34+ cells ($\times 10^6$/kg)	5.5 (3.1-15.2) (n=10)	9.4 (2.9-36.8) (n=9)	0.11
CFU-GM ($\times 10^4$/kg)	22.4 (3.4-49.8) (n=8)	9.9 (2.6-21.5) (n=10)	0.05
Number of leukapheresis sessions required to obtain a CD34+ cells > 2×10^6/kg	9.5 (0.7-52.0) (n=10)	13.0 (0.8-41.6) (n=9)	0.97
1	10 (100%)	6 (67%)	0.09
2		3 (33%)	

(n=9 patients) and 12×10^6/L (95% CI : 5-19$\times 10^6$/L) in arm B (n=8 patients). In arm A, the CD34+ cell count decreased slowly and reached the nadir on day 7; after that time, it increased rapidly. In arm B, it was difficult to find the distinct change, but the CD34+ cell count exhibited a tendency to increase somewhat from day 10. The CD34+ cell count reached the peak of 77×10^6/L (95% CI : 43-112$\times 10^6$/L) on days 9-14 in arm A, and the CD34+ cell count reached the peak of 31×10^6/L (95% CI : 22-40$\times 10^6$/L) on days 9-12 in arm B.

The mean CFU-GM in the PB prior to CY administration was 60.5×10^3/L (95% CI : 8.8-111.2$\times 10^3$/L) in arm A (n=9) and it was 79.5×10^3/L (95% CI : 0-164.6$\times 10^3$/L) in arm B (n=8). In arm A, the CFU-GM decreased slowly and it reached the nadir on day 7. After that time, it increased rapidly. In arm B, it decreased somewhat lower than at the baseline and it reached the nadir on day 5; it then increased rapidly. The CFU-GM reached a peak of 499.9×10^3/L (95% CI : 280.3-719.4$\times 10^3$/L) on days 10-16 in arm A, and the CFU-GM reached a peak of 547.2×10^3/L (95% CI : 142.0-952.4$\times 10^3$/L) on days 8-12 in arm B.

Leukapheresis and yield

The efficacy of the two methods of mobilization is summarized in table 2. The patients in arm A began leukapheresis at a median of 10 days (range: 9-13 days) after CY administration, and the patients in arm B began leukapheresis a median of 9 days (range: 7-11 days) (p=0.02). The median number of leukapheresis sessions that were actually done was 2.5 (range: 2-5 sessions) in arm A and 3 (range: 2-4 sessions) in arm B (p=0.3). The median amount of blood that was processed during leukapheresis was 49.3 liters (range: 30-85 liters) in arm A and 48.7 liters (range: 30-69 liters) in arm B (p=0.8).

The median number of MNCs collected with performing leukapheresis was 5.5×10^8/kg (range: 3.1-15.2$\times 10^8$/kg) in arm A and 9.4×10^8/kg (range: 2.9-36.8$\times 10^8$/kg) in arm B. The median number of CD34+ cells collected was 22.4×10^6/kg (range: 3.1-15.2$\times 10^6$/kg, n=10 patients in arm A, and 9.9×10^6/kg (range: 2.9-36.8$\times 10^6$/kg, n=9 patients) in arm B (p=0.05). The yield of CD34+ cells that were collected showed a strong

Table 3. Toxicity during mobilization

	Grade	Arm A (n=15)	Arm B (n=12)	*p* value
Leukopenia	III	1 (7%)	1 (8%)	<0.0001
	IV	13 (87%)	0	
Thrombocytopenia	III	7 (47%)	0	0.0004
	IV	1 (7%)	0	
Nausea/vomiting	II	4 (27%)	1 (8%)	0.3
	III	1 (8%)	0	
Fever (≥38℃)		6 (40%)	1 (8%)	0.09

correlation with the pre-apheresis CD34+ cell count in the PB. The correlation coefficient for the number of CD34+ cells in the PB with the number of CD34+ cells in the leukapheresis products was 0.6 (p=0.02). The median number of CFU-GM collected was 9.5×10^4/kg (range; 0.7-52.0$\times10^4$/kg, n=8 patients) in arm A, and it was 13.0×10^4/kg (range: 0.8-41.6$\times10^4$/kg, n=10 patients) in arm B (p=0.97).

There was no statistically significant difference in the number of leukapheresis sessions required for the collection of the target number of CD34+ cells (p=0.09). All 10 patients in arm A whose CD34+ cell counts were measured had the cells collected in one leukapheresis session. Of the 9 patients in arm B whose CD34+ cell counts were measured, 6 patients (67%) had the cells collected in one session and 3 patients (33%) had the cells collected in two sessions, respectively.

Toxicity

There were no treatment-related deaths during mobilization. The major toxicities are summarized in table 3. Grade III or IV (WHO) leukopenia was present in 14 patients (94%) in arm A versus 1 patient (8%) in arm B (p<0.0001). Grade III or IV thrombocytopenia was present in 8 patients (54%) in arm A, but there was no grade III or IV thrombocytopenia in arm B (p=0.0004). Grade II nausea and vomiting was observed in 4 patients (27%) and grade III nausea and vomiting was observed in 1 patient (8%) in arm A, while one patient (8%) showed grade II nausea and vomiting in arm B (p=0.3). Neutropenic fever over 38℃ occurred for 6 patients (40%) in arm A, and for 1 patient (8%) in arm B (p=0.09).

Engraftment

Autologous PBPC transplantation after mobilization was done for 14 out of 15 patients in arm A, and for 11 out of 12 patients in arm B. There were no graft failures in both arms of the study. There was no significant difference found in the time to hematopoietic recovery after transplantation between the two arms. The median time to an ANC ≥0.5×10^9/L was 9.5 days (range: 8-16 days) in arm A, and 11 days (range: 9-12 days) in arm B (p=0.1). The median time to a platelet count ≥20×10^9/L was 8 days (range: 1-34 days) in arm A and 11 days (range: 1-16 days) in arm B (p=0.4). There was no significant difference in the number of CD34+ cells infused during transplantation: it was 9.5×10^6/kg (range: 1.5-26.8$\times10^6$/kg) in arm A and 8.4×10^6/kg (range: 2.6-13.9$\times10^6$/kg) in arm B (p=0.3). There was no significant difference in the duration of lenograstim administration after transplantation: it was 11 days (range: 9-24 days) in arm A and 12 days (range: 9-14 days) in arm B. The number of CD34+ cells/kg that were infused correlated with a more rapid neutrophil recovery (r=-0.6, p=0.009).

DISCUSSION

For all the categories of the mobilization protocols, the amount of previous chemoradiotherapy is one of the most significant determinants of the progenitor cell yield[9]. To evaluate the efficacy of the mobilization protocols, it may be reasonable to enroll the patients who were exposed to only a small amount of chemoradiotherapy. So, we performed this study with enrolling the newly diagnosed high-risk NHL or BC patients who were planning to undergo HDC with autologous SCT after only 3-4 cycles of induction or adjuvant chemotherapy. When the study was first designed in 1998, there were several promising phase II studies being done on autologous SCT for high-risk NHL or BC[12-16]. However, the patient accrual was gradually reduced and the study was prematurely closed, in part because the popularity for autologous SCT in these settings has subsided.

Many investigators have used disease-specific chemotherapy for mobilization, although this may not be universally applicable to all patients. High-dose CY (3-7 g/m^2) has also been extensively used. The major problem with CY-induced mobilization at this dosage is the drug-related toxicity. Patients who were treated with 4 g/m^2 CY had a 50% hospitalization rate for febrile neutropenia and the rate was 100% for patients treated with 7 g/m^2 CY[17]. We also observed that 40% of the patients mobilized with 4 g/m^2 CY developed neutropenic fever and they needed treatment with antibiotics. However, only 8% of the patients mobilized with 1.5 g/m^2 CY developed neutropenic fever. There were actually no cases of severe thrombocytopenia

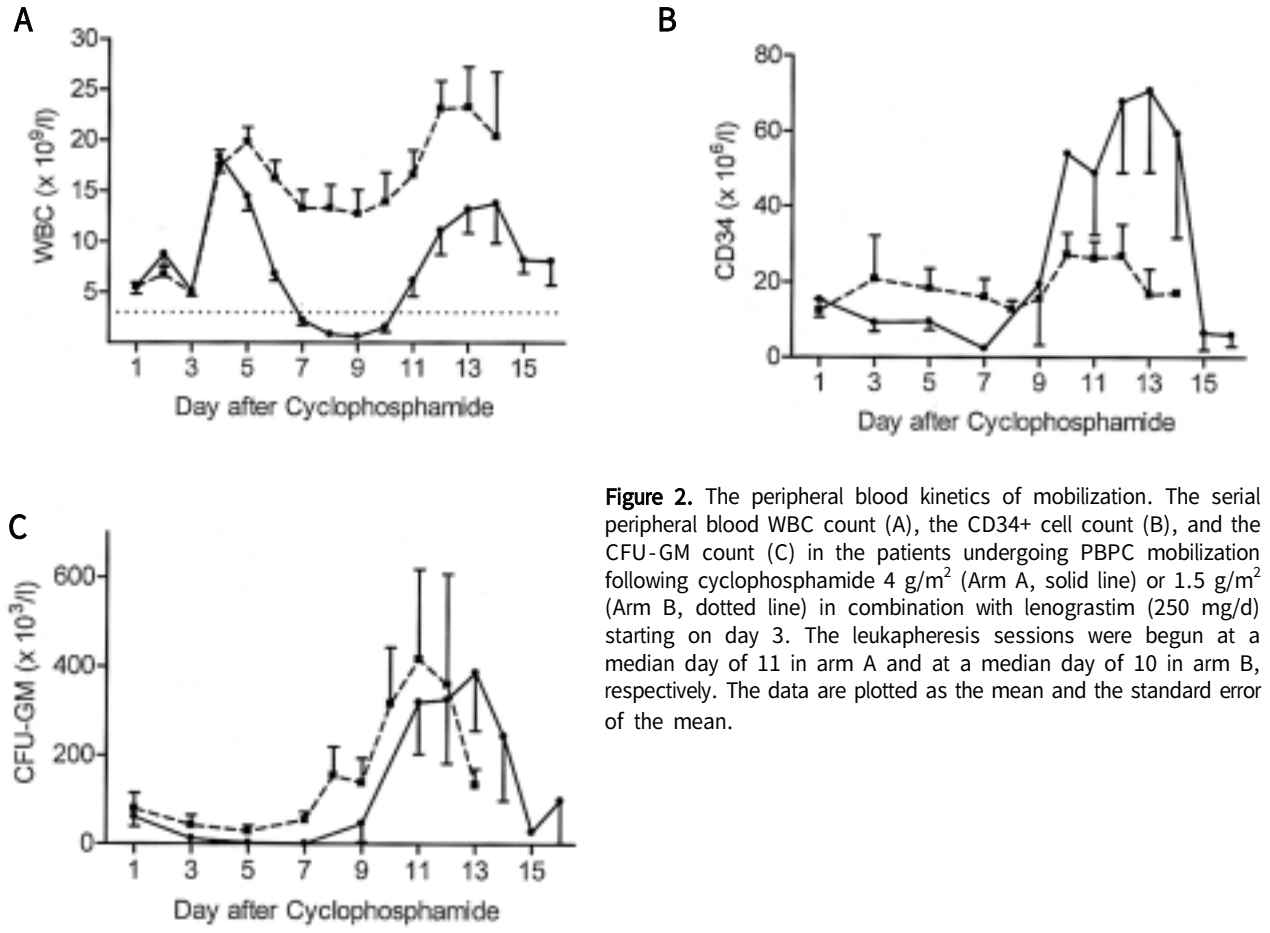

Figure 2. The peripheral blood kinetics of mobilization. The serial peripheral blood WBC count (A), the CD34+ cell count (B), and the CFU-GM count (C) in the patients undergoing PBPC mobilization following cyclophosphamide 4 g/m^2 (Arm A, solid line) or 1.5 g/m^2 (Arm B, dotted line) in combination with lenograstim (250 mg/d) starting on day 3. The leukapheresis sessions were begun at a median day of 11 in arm A and at a median day of 10 in arm B, respectively. The data are plotted as the mean and the standard error of the mean.

and the other toxicities were also milder in the low-dose CY arm. Low-dose CY was very safe from the viewpoint of toxicity, and the cost was lower due to reduced use of antibiotics and transfusions. Adequate PBPC mobilization is expected to be possible on an outpatient basis and this could further reduce the cost of the procedure.

All the patients in the high-dose CY arm whose CD34+ cell counts were measured needed a single leukapheresis session to get the targeted collection, whereas 33% of the patients in the low-dose CY arm needed two sessions. However, most of the participating clinicians carried out at least 2 leukapheresis sessions even though the targeted cell dose was obtained in one leukapheresis session. Thus, low-dose CY practically appears to be similar to the high-dose CY for the number of apheresis sessions required for the targeted collection.

High-dose CY increased the number of PB CD34+ cells and the CFU-GM about 5-fold and 8-fold over the baseline, respectively. The corresponding figures in the low-dose CY arm were 2.5-fold and a 7-fold increase over the baseline, respectively. A greater increase of the PB CD34+ cell count in the high-dose CY arm resulted in a significantly greater CD34+ cell yield of the apheresis products. The mean number of CD34+ cells collected in the high-dose CY arm was about 2 times higher than that in the low-dose CY arm. On the other hand, the increase of the CFU-GM in the PB was comparable for the two groups, and the yields of the CFU-GM in the apheresis products were similar. This discrepancy may be due to the heterogeneity of the CD34+ cell population. Although CD34+ cells have been used as the best phenotypic marker of the hematopoietic stem cells used for transplantation, this population is not homogeneous. Only about 1% or less of the CD34+ cells represents the hematopoietic stem cells[18]. The heterogeneous CD34+ cell populations represent different CD34+ subsets such as the primitive stem cells, the early myeloid cells, the late myeloid cells and the late erythroid cells[19].

The timing of PBPC collection has not yet been established, but most medical groups start apheresis when the leukocyte count is 2 to 5×10^9/L during the chemotherapy and the hematopoietic growth factor mobilization. We started apheresis when the WBC count reached above 3×10^9/L after the nadir. The CD34+ cell counts in the PB at this point were mostly over

30×10^6/L in the high-dose CY arm, and this enabled us to collect the targeted cells with a single apheresis session[20]. In the low-dose CY arm, the WBC count did not fall below 3×10^9/L except for one patient, and we started apheresis when the WBC count began to increase after the nadir. The CD34+ cell counts in the PB at this point were lower than those in the high-dose CY arm, but they were in accord with one of the highest points. Thus, the timing of the PBPC collection in both arms seemed to be adequate.

Engraftment after transplantation was similar in the two mobilization groups. Although the CD34+ cell content has been correlated with the time to engraftment, there is a threshold effect beyond which the cell number does not appear to make a difference[21, 22]. Thus, it may be unnecessary to collect PBPCs above a certain level. However, high-dose CY may be beneficial if the primary goal is to collect the CD34+ cells for manipulation, such as for gene therapy or for in vitro expansion or selection.

In conclusion, mobilization with low-dose CY plus lenograstim is an effective regimen with very mild toxicity in comparison to high-dose CY. These results will translate into more effective cost control and better resource utilization. However, high-dose CY plus lenograstim may be beneficial when a high number of CD34+ cells is required.

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