Biol Blood Marrow Transplant 20 (2014) 73–79

High-Dose Etoposide Plus Granulocyte Colony-Stimulating Factor as an Effective Chemomobilization Regimen for Autologous Stem Cell Transplantation in Patients with Non-Hodgkin Lymphoma Previously Treated with CHOP-based Chemotherapy: A Study from the Consortium for Improving Survival of Lymphoma

Shin Young Hyun [1], June-Won Cheong [1], Soo-Jeong Kim [1], Yoo Hong Min [1], Deok-Hwan Yang [2], Jae-Sook Ahn [2], Won-Sik Lee [3], Hun-Mo Ryoo [4], Young Rok Do [5], Ho Sup Lee [6], Jae Hoon Lee [7], Sung Yong Oh [8], Cheolwon Suh [9], Ho-Young Yhim [10], Jin Seok Kim [1,*]

[1] *Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, Korea*
[2] *Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, Korea*
[3] *Inje University College of Medicine, Busan Paik Hospital, Busan, Korea*
[4] *Daegu Catholic University Medical Center, Daegu, Korea*
[5] *Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea*
[6] *Kosin University Gospel Hospital, Busan, Korea*
[7] *Gachon University Gil Medical Center, Incheon, Korea*
[8] *Dong-A University College of Medicine, Busan, Korea*
[9] *Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*
[10] *Chonbuk National University Medical School, Jeonju, Korea*

Article history:
Received 29 May 2013
Accepted 11 October 2013

Key Words:
Cyclophosphamide
Etoposide
Platinum
Stem cell mobilization
Non-Hodgkin lymphoma

A B S T R A C T

We conducted a multicenter retrospective study to compare the efficacy and toxicity of various chemomobilization regimens: high-dose (HD) cyclophosphamide, HD etoposide (VP-16), and platinum-based chemotherapies. We reviewed the experiences of 10 institutions with 103 non-Hodgkin lymphoma patients who had previously only been treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based chemotherapy. The mobilization yields for each regimen were analyzed. HD VP-16 mobilized a significantly higher median number of $CD34^+$ cells (16.22×10^6 cells/kg) than HD cyclophosphamide (4.44×10^6 cells/kg) or platinum-based chemotherapies (6.08×10^6 cells/kg, $P < .001$). The rate of successful mobilization ($CD34^+$ cell count $\geq 5.0 \times 10^6$ cells/kg) was also significantly higher for HD VP-16 (86%) than for HD cyclophosphamide (45%) or platinum-based chemotherapies (61%, $P = .004$). The successful mobilization rate on day 1 of 72% for HD VP-16 was significantly higher than the rates for HD cyclophosphamide (13%) and platinum-based chemotherapies (26%, $P < .001$). In multivariate analysis, HD VP-16 was a significant predictor of successful mobilization ($P = .014$; odds ratio, 5.25; 95% confidence interval, 1.40 to 19.63). Neutropenic fever occurred in 67% of patients treated with HD VP-16. The incidence was similar for HD cyclophosphamide (58%, $P = .454$) but was significantly lower for platinum-based chemotherapies (12%, $P < .001$). However, fatal (grade ≥ 4) infection and treatment-related mortality were not observed in this study. In conclusion, the mobilization yield was significantly influenced by the chemomobilization regimen, and HD VP-16 was a highly effective mobilization regimen in patients with non-Hodgkin lymphoma.

INTRODUCTION

High-dose (HD) chemotherapy followed by autologous stem cell transplantation (ASCT) is a curative treatment option for patients with non-Hodgkin lymphoma (NHL) [1,2]. For successful ASCT, it is essential to collect a sufficient number of peripheral blood stem cells (PBSCs). Various chemomobilization regimens have been used in patients with NHL. HD cyclophosphamide or platinum-based chemotherapies such as ifosfamide/carboplatin/etoposide (ICE), cisplatin/cytarabine/dexamethasone (DHAP), and etoposide/methylprednisolone/cytarabine/cisplatin (ESHAP) are commonly used in combination with recombinant granulocyte colony-stimulating factor (G-CSF) [3-7]. Etoposide (VP-16) has also been considered an effective chemotherapeutic agent for PBSC mobilization [8]. The efficacy and the toxicity of HD VP-16 for chemomobilization have been reported in patients with NHL and multiple myeloma [9-11]. Although several studies have compared the efficacy of platinum-based chemotherapies and HD cyclophosphamide in terms of mobilization yield [4-6], few studies have verified the clinical efficacy of HD VP-16 compared with other regimens.

Mobilization failure has significant consequences, such as potential loss of ASCT as a treatment option. Repeated mobilization attempts increase medical costs and morbidity/mortality risks. Therefore, it is extremely important to determine the best chemomobilization regimen [1,12].

Financial disclosure: See Acknowledgments on page 78.

* Correspondence and reprint requests: Jin Seok Kim, MD, PhD, Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
E-mail address: hemakim@yuhs.ac (J.S. Kim).

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.10.012

However, it is very difficult to evaluate the direct effect of chemotherapy on mobilization yield in the context of relapsed NHL, because apheresis is usually performed after various salvage chemotherapies such as ICE, DHAP, and ESHAP and prior use of platinum compounds or alkylating agents is closely related to poor mobilization [13]. Therefore, we selected patients with NHL who had previously only been treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab-CHOP (R-CHOP) chemotherapy and who had not experienced relapse or progression. We conducted a retrospective multicenter study to determine the impact of various chemomobilization regimens, including HD cyclophosphamide, HD VP-16, and platinum-based chemotherapies, on PBSC mobilization in NHL patients only exposed to CHOP-based chemotherapy.

METHODS

Patient Eligibility

One hundred three patients from 10 institutions in Korea were included by retrospective review of medical records. Patients diagnosed with NHL who underwent PBSC mobilization for ASCT between January 2005 and December 2011 were included. CHOP or R-CHOP chemotherapy was allowed as previous chemotherapy and at least a partial response to CHOP-based chemotherapy was required. We excluded patients who (1) had received chemotherapeutic drugs other than CHOP or R-CHOP before PBSC mobilization, (2) were aged under 20 or over 65 years, (3) had a history of prior PBSC mobilization attempts, and/or (4) had a history of malignancies other than NHL. The protocol was approved by each institution's institutional review board.

PBSC Mobilization Protocol

For PBSC mobilization, 5 different chemomobilization regimens were used. Patient characteristics are summarized in Table 1. Thirty-one patients received HD cyclophosphamide (4.0 g/m^2/day, i.v.) on day 1. Twenty-nine patients received HD VP-16 (500 mg/m^2/day) as 2 doses (i.v.) over 4 hours on days 1 to 3. Ten patients received an ICE regimen consisting of 5.0 g/m^2/day ifosfamide on day 2, carboplatin on day 2 at a dose calculated using the Calvert formula (5 × [creatinine clearance + 25]; maximum dose 800 mg), and 100 mg/m^2/day etoposide on days 1 to 3. Twenty-one patients received a DHAP regimen consisting of 100 mg/m^2/day cisplatin on day 1, 4.0 g/m^2/day cytarabine on day 2, and 40 mg/day dexamethasone on days 1 to 4. Twelve patients received an ESHAP regimen consisting of 40 mg/m^2/day etoposide on days 1 to 4, 500 mg/day methylprednisolone on days 1 to 5, 2.0 g/m^2/day cytarabine on day 5, and 25 mg/m^2/day cisplatin on days 1 to 4. G-CSF (10 μg/kg/day) was subcutaneously administered from 1 day after the completion of mobilization chemotherapy until the last day of apheresis. Chemotherapy-related toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [14].

To determine the first day of apheresis, the white blood cell (WBC) count was monitored daily after the completion of chemotherapy and the number of peripheral blood CD34$^+$ cells or number of peripheral blood hematopoietic progenitor cells was also monitored according to each institution's policy. PBSC collection was usually initiated when the peripheral blood CD34$^+$ cell or peripheral blood hematopoietic progenitor cell count was at least 5 × 10^6/L. We also analyzed the mobilization results in patients who had no information about the peripheral blood CD34$^+$ cell count or hematopoietic progenitor cell count on the first day of apheresis (68 of 103 patients). If the peripheral blood CD34$^+$ cell or peripheral blood hematopoietic progenitor cell count could not be used to determine the first day of apheresis, apheresis was mostly started on the first day with a WBC count of >5.0 × 10^9/L. Although the apheresis procedure was performed according to each institution's policy, most apheresis procedures processed a minimum of 2 times the total blood volumes per day for more than 2 hours. Before cryopreservation, the collected PBSCs were analyzed for CD34 expression by flow cytometry. Apheresis was usually continued until sufficient numbers of CD34$^+$ cells for ASCT had collected.

Autologous Stem Cell Transplantation

Ninety-five patients (92%) underwent frontline ASCT. Six patients did not receive ASCT because of failed PBSC mobilization (median CD34$^+$ cell count: 0.12 × 10^6 cells/kg), and 2 patients did not receive ASCT because of personal reasons. The preparative regimens for ASCT and supportive care

Table 1
Patient Characteristics According to Mobilization Regimen

	HD CTX	HD VP-16	Platinum-Based Chemotherapy (n = 43)			*P*
			ICE	DHAP	ESHAP	
Number of patients	31	29	10	21	12	
Median age, yr (range)	46 (22-61)	52 (19-62)	45 (17-61)	50 (23-65)	57 (15-64)	.094
Male gender	13 (42%)	17 (59%)	4 (40%)	14 (67%)	8 (67%)	.848
Histology (B cell vs. T cell)						.005
B cell subtype	26 (84%)	29 (100%)	7 (70%)	14 (67%)	12 (100%)	
Diffuse large B cell lymphoma	24	26	7	11	10	
Thymic large B cell lymphoma	1	1		1		
Mantle cell lymphoma	1	1		2	1	
B cell lymphoma, unclassifiable		1				
Nodal marginal zone lymphoma					1	
T cell subtype	5 (16%)	0	2 (20%)	7 (33%)	0	
Anaplastic large cell lymphoma	1		1	2		
Peripheral T cell lymphoma, NOS	2		1	4		
Angioimmunoblastic T cell lymphoma	2					
Subcutaneous panniculitis-like T cell lymphoma			1	1		
Ann Arbor stage						.008
II, bulky disease	2 (7%)	1 (3%)	0	2 (10%)	2 (17%)	
III	7 (22%)	1 (3%)	1 (10%)	10 (48%)	4 (33%)	
IV	22 (71%)	27 (93%)	9 (90%)	9 (43%)	6 (50%)	
BM involvement at diagnosis	10 (32%)	7 (25%)	3 (30%)	3 (14%)	6 (50%)	.255
IPI score ≥3*	17 (55%)	8 (73%)	2 (40%)	17 (55%)	6 (40%)	.423
Number of previous chemotherapy cycles, median (range)	6 (4-8)	6 (3-8)	6 (6-8)	6 (6-8)	6 (5-7)	.072
Previous radiation therapy	4 (13%)	2 (7%)	1 (10%)	0	0	.501
Previous use of rituximab	26 (84%)	28 (97%)	8 (80%)	16 (76%)	9 (75%)	.257
Disease status before mobilization						.008
Complete remission	24 (77%)	12 (41%)	4 (40%)	17 (81%)	7 (58%)	
Partial remission	7 (23%)	17 (59%)	6 (60%)	4 (19%)	5 (42%)	
Days from last chemotherapy to start of mobilization chemotherapy (range)	30 (21-385)	31 (20-154)	39 (26-82)	34 (21-81)	29 (19-396)	.424
Median follow-up duration after mobilization start, mo (range)	17 (1-57)	26 (8-63)	39 (11-64)	15 (1-68)	35 (2-50)	.162

NOS indicates not otherwise specified; BM, bone marrow; IPI, international prognostic index.
* IPI score was missed in 29 patients of 103 patients.

after ASCT were decided by the protocol of each institution. Most patients (90%) received intravenous busulfan-based preparation regimens such as busulfan/cyclophosphamide/etoposide (n = 30), busulfan/cytarabine/etoposide/melphalan (n = 21), busulfan/thiotepa (n = 20), and busulfan/melphalan/etoposide (n = 14). Ten percent of patients received another preparative regimen (eg, mitoxantrone/etoposide/cytarabine/melphalan). G-CSF (5 μg/kg/day) was used after PBSC infusion and was continued until the neutrophil count recovered to at least 1.0×10^9/L on 2 consecutive days. Platelet transfusion was performed if the platelet count fell below 2.0×10^9/L or if clinically significant bleeding occurred.

Statistical Analysis

The efficacy of PBSC mobilization and chemomobilization-related toxicities were analyzed according to the chemomobilization regimens. To simplify the statistical analysis, we classified the patients into 3 groups: patients who received HD cyclophosphamide (CTX group), patients who received HD VP-16 (VP-16 group), and patients who received ICE, DHAP, or ESHAP (platinum-based chemotherapy group). We defined successful mobilization as a mobilized $CD34^+$ cell count $\geq 5.0 \times 10^6$/kg, adequate mobilization as a mobilized $CD34^+$ cell count $\geq 2.0 \times 10^6$/kg, and failure of mobilization as a mobilized $CD34^+$ cell count $< 2.0 \times 10^6$/kg. Neutrophil engraftment after PBSC infusion was defined as the first of 3 consecutive days with a neutrophil count $> .5 \times 10^9$/L and platelet engraftment as the first of 3 days with an unsupported platelet count $> 20 \times 10^9$/L. Progression-free survival, overall survival, complete response, and partial response were defined according to the International Working Group criteria for responses in NHL [15].

Categorical variables were compared between the groups using the chi-square test. Multiple comparisons of continuous variables were conducted using the Kruskal-Wallis test. Continuous variables were also compared between the 2 groups using the Wilcoxon rank-sum test. Univariate and multivariate analyses of successful mobilization and successful mobilization on day 1 were performed using logistic regression models. Survival data were analyzed using the Kaplan-Meier method, and survival curves were compared using the log-rank test. $P < .05$ was defined as statistically significant. All statistical calculations were performed with PASW software, version 20.0 (SPSS, Inc, Chicago, IL).

RESULTS

Patient Characteristics

The clinical characteristics of patients are summarized according to chemomobilization regimen in Table 1. Age, gender, international prognostic index score ≥3, and bone marrow involvement at the time of diagnosis were comparable among the groups. Patients with advanced disease (stage IV) were more common in the VP-16 and ICE groups ($P = .008$), and complete response status before chemomobilization was more frequently observed in the CTX and DHAP groups ($P = .008$). However, the premobilization clinical characteristics of these patients were similar in terms of number of previous chemotherapy courses, previous use of rituximab, previous exposure to radiation therapy, and time from last chemotherapy to start of chemomobilization.

PBSC Mobilization and Mobilization Yields

The median time from the first day of chemotherapy for mobilization to apheresis was shorter in the CTX and platinum-based chemotherapy groups than in the VP-16 group ($P = .020$, Table 2). However, the median number of days of apheresis was significantly lower in the VP-16 group (1 day) than in other groups (3 days) ($P < .001$). Based on the 35 available peripheral blood $CD34^+$ cell counts for the first day of apheresis, the VP-16 group also showed a significantly higher count than the other groups (110×10^6/L versus 9.5×10^6/L, $P = .010$). The VP-16 group had a significantly higher mobilization yield (16.22×10^6 $CD34^+$ cells/kg) than the other groups (4.44×10^6 $CD34^+$ cells/kg for the CTX group, 6.08×10^6 $CD34^+$ cells/kg for the platinum-based chemotherapy group, $P < .001$). The VP-16 group showed the highest number of $CD34^+$ cells collected on day 1 ($P < .001$) as well as the highest number of $CD34^+$ cells collected on days 1 and 2 ($P < .001$). In addition, the number of $CD34^+$ cells collected per day of apheresis was highest in the VP-16 group ($P < .001$).

The rate of successful mobilization was highest in the VP-16 group (86%, $P = .004$, Table 3). Successful mobilization was observed in 61% of patients who received platinum-based chemotherapies and in only 45% of patients who received cyclophosphamide chemotherapy. Successful mobilization rate on day 1 (72%) and successful mobilization rate within the first 2 days (76%) were significantly higher in the VP-16 group than in the other groups ($P < .001$ and $P = .002$, respectively). Time to successful mobilization was significantly shorter in the VP-16 group ($P < .001$ [log-rank test], Figure 1). Although there were no statistical differences in rate of adequate mobilization, the VP-16 group showed a significantly higher rate of adequate mobilization on day 1 ($P = .009$). In the VP-16 group, no patients experienced mobilization failure and mobilization failure tended to be less frequent compared with the other groups ($P = .051$).

Chemomobilization regimen and WBC count on the first day of apheresis $\geq 10 \times 10^9$/L were significant variables for successful mobilization in univariate analysis (Table 4). Multivariate analysis showed that successful mobilization was independently influenced by chemomobilization regimen, especially HD VP-16 ($P = .014$; odds ratio, 5.25; 95% confidence interval [CI], 1.40 to 19.63). High WBC count on the first day of apheresis ($\geq 10 \times 10^9$/L) also showed statistical significance ($P = .032$; odds ratio, 3.85; 95% CI, 1.12 to 13.24). Because peripheral blood $CD34^+$ cell counts on the first day of apheresis were only available for 35 patients, we decided to exclude this factor from the analyses. In univariate analysis, the predictive factors for successful mobilization on day 1 were age <50 years, male gender, chemomobilization with HD VP-16, and high WBC count on the first day of apheresis (Table 4). In multivariate analysis of successful mobilization on day 1, chemomobilization with HD VP-16 was the only significant variable ($P < .001$; odds ratio, 17.72; 95% CI, 4.69 to 66.92).

Table 2
Outcomes of Stem Cell Mobilization

	HD CTX (n = 31)	HD VP-16 (n = 29)	Platinum-Based Chemotherapy (n = 43)	*P*
Days from mobilization chemotherapy to apheresis	13 (10-18)	15 (13-19)	14 (6-20)	.020
Peripheral blood $CD34^+$ cell count on the first day of apheresis, $\times 10^6$/L*	10 (5-15)	110 (1-1415)	9.5 (0-406)	.028
Number of days of apheresis	3 (1-9)	1 (1-6)	3 (1-7)	.004
Total number of $CD34^+$ cells collected, $\times 10^6$/kg	4.44 (.20-35.50)	16.22 (3.37-151.47)	6.08 (.02-38.94)	<.001
$CD34^+$ cells collected on day 1, $\times 10^6$/kg	1.20 (.09-20.90)	15.37 (.17-151.47)	1.57 (.00-23.00)	<.001
$CD34^+$ cells collected on days 1 + 2, $\times 10^6$/kg	2.66 (.10-33.82)	16.22 (.75-151.47)	4.29 (.02-23.00)	<.001
$CD34^+$ cells collected per apheresis, $\times 10^6$/kg	1.15 (.07-16.91)	15.37 (.56-151.47)	3.00 (.02-23.00)	<.001

* Peripheral $CD34^+$ cell count on the first day of apheresis was missed in 68 patients of 103 patients.

Table 3
Mobilization Efficacy

	HD CTX (n = 31)	HD VP-16 (n = 29)	Platinum-Based Chemotherapy (n = 43)	*P*
Successful mobilization ($\geq 5 \times 10^6$/kg)	14 (45%)	25 (86%)	26 (61%)	.004
Successful mobilization on day 1	4 (13%)	21 (72%)	11 (26%)	<.001
Successful mobilization on days 1 + 2	10 (32%)	22 (76%)	19 (44%)	.002
Adequate mobilization ($\geq 2 \times 10^6$/kg)	25 (81%)	29 (100%)	38 (88%)	.051
Adequate mobilization on day 1	12 (39%)	22 (76%)	20 (47%)	.009
Mobilization failure ($< 2 \times 10^6$/kg)	6 (19%)	0	5 (12%)	.051

Toxicities of Chemomobilization

Chemomobilization-induced neutrophil nadir developed a median of 10 days after HD VP-16 or HD cyclophosphamide chemotherapy and was significantly delayed in the platinum-based chemotherapy group (12 days, $P < .001$, Table 5). Absolute neutrophil count at nadir was higher in the platinum-based chemotherapy group ($P < .001$). Duration of absolute neutrophil count $< .5 \times 10^9$/L and duration of G-CSF administration were longer in the VP-16 group than in the other groups ($P < .001$ and $P < .001$, respectively). In addition, platelet count at nadir was also significantly lower in the VP-16 group ($P = .010$). Neutropenic fever occurred in 67% of patients treated with HD VP-16. The incidence of neutropenic fever was similar in the CTX group (58%, $P = .454$) but significantly lower in the platinum-based chemotherapy group (12%, $P < .001$). However, fatal (grade ≥ 4) infection and treatment-related mortality were not observed in this study (Table 5).

Transplantation and Survival

A higher number of collected $CD34^+$ cells were infused for ASCT in the VP-16 group compared with the other groups ($P < .001$, Table 6). The median time to neutrophil engraftment and platelet engraftment did not differ according to chemomobilization regimen. At a median follow-up of 26 months after chemomobilization, there were no differences in progression-free survival or overall survival among the different chemomobilization regimens used, and there were no reports of therapy-related myelodysplastic syndrome/acute myeloid leukemia (tMDS/AML) in any group.

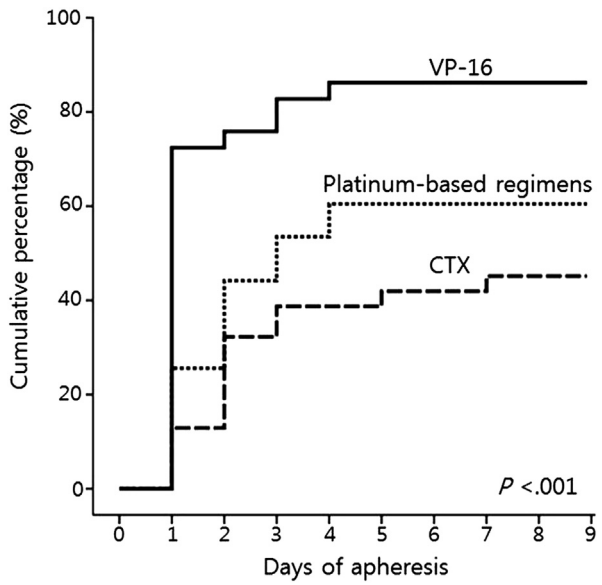

Figure 1. Days to collect $CD34^+$ cells $\geq 5.0 \times 10^6$ cells/kg. CTX indicates high-dose cyclophosphamide; VP-16, high-dose etoposide.

DISCUSSION

Among various chemotherapy regimens for PBSC mobilization, we demonstrated that HD VP-16 was the most effective chemomobilization regimen in terms of mobilization yield. Moreover, the HD VP-16 regimen achieved successful mobilization within a minimum number of days of apheresis. Although the incidence of neutropenic fever was higher in the VP-16 group, it might be acceptable because no patient had a grade 4 infection and there was no treatment-related mortality.

PBSC mobilization yield is influenced by various factors, including age, underlying disease, prior chemotherapies, disease status, bone marrow involvement at diagnosis, peripheral $CD34^+$ cell count, and platelet count just before mobilization [1,13,16-20]. Previous exposure to chemotherapeutic agents such as platinum compounds or alkylating agents and a higher number of prior chemotherapy courses were considered to be especially important predictors of poor mobilization yield [13,21]. Although several studies have reported on the efficacy of various chemomobilization regimens, they have usually included patients with various underlying diseases and various previous chemotherapeutic agents, such as platinum compounds and alkylating agents [22]. Under such conditions, it is very difficult to evaluate the impact of chemotherapy regimens for PBSC mobilization on mobilization yield. In the present study, to minimize the confounding effects of prior chemotherapies, we selected patients with NHL who had previously only been treated with CHOP or R-CHOP chemotherapy. This enabled us to evaluate the direct effects of various chemomobilization regimens on mobilization yield.

Because PBSC mobilization with G-CSF alone showed comparable mobilization results in patients who received less intensive pretreatment [23], we might consider G-CSF alone in our patients. However, we wanted to evaluate the impact of various chemomobilization regimens on PBSC mobilization in NHL patients. Therefore, we did not include patients who received G-CSF alone for PBSC mobilization in this study. HD cyclophosphamide and salvage chemotherapies such as ICE, DHAP, and ESHAP have been commonly used for PBSC mobilization in patients with NHL. Although DHAP and ESHAP regimens did not show superior results to an HD cyclophosphamide regimen [4,5], another study with an ESHAP regimen reported a higher mobilization yield in the ESHAP group compared with the HD cyclophosphamide group [6]. Therefore, the optimal chemomobilization regimen for NHL has not yet been determined.

VP-16 has been widely used in combination with other chemotherapeutic drugs for the treatment of malignant lymphoma and has also been effectively used for chemomobilization [8-11,24-26]. Although HD VP-16 (2.0 g/m^2)

Table 4
Univariate and Multivariate Analysis of Successful Mobilization and Successful Mobilization on Day 1

Variables	Successful Mobilization			Successful Mobilization on Day 1		
	Univariate	Multivariate		Univariate	Multivariate	
	P	*P*	Odds Ratio (95% CI)	*P*	*P*	Odds Ratio (95% CI)
Mobilization regimen (vs. HD cyclophosphamide)	.591	.037		<.001	<.001	
HD etoposide	.002	.014	5.25 (1.40-19.63)	<.001	<.001	17.72 (4.69-66.92)
Platinum-based chemotherapy	.194	.758	1.18 (.41-3.36)	.188	.066	3.38 (.92-12.33)
Age <50 years	.224			.043	.323	1.69 (.60-4.76)
Male gender	.476			.007	.825	1.12 (.40-3.14)
Ann Arbor stage II or III (vs. IV)	.882			.209		
Absence of BM involvement at diagnosis	.298			.602		
No previous radiation therapy	.638			.261		
Previous use of rituximab	.956			.151		
Number of chemotherapy cycles (<6 cycles)	.535			.691		
Interval from last chemotherapy (<1 mo)	.372			.298		
CR status before mobilization (vs. PR)	.797			.314		
WBC count on the first day of apheresis ($\geq 10 \times 10^9$/L)	.004	.032	3.85 (1.12-13.24)	.003	.084	2.65 (.88-8.00)
Platelet count on the first day of apheresis ($\geq 15 \times 10^9$/L)	.505			.224		
Peripheral blood CD34$^+$ cells on the first day of apheresis ($\geq 20 \times 10^6$/L)*	Not assessable			Not assessable		

BM indicates bone marrow; CR, complete remission; PR, partial remission.
* Because of the high rate of missing data, we excluded this factor from univariate and multivariate analyses.

may increase the risk of developing tMDS/AML after ASCT [27], Mahindra et al. [9] reported significantly higher mobilization yields in patients who received HD VP-16 for PBSC mobilization compared with those who received G-CSF alone, without an increased risk of tMDS/AML. In addition, HD VP-16 was shown to be an effective chemomobilization regimen for patients in whom initial mobilization with HD cyclophosphamide failed [25]. VP-16, at a dose of either 1.5 or 1.0 g/m^2 [26] or an intermediate dose (750 or 600 mg/m^2) [11,24], has also been effective for chemomobilization in previous studies. Although an intermediate dose of VP-16 (200 mg/m^2/day for 3 days) may be superior to HD cyclophosphamide in terms of mobilization yield [24], no studies have compared the mobilization yields of these various chemomobilization regimens, including HD VP-16 and platinum-based chemotherapies. In the present study, we selected patients who had received HD cyclophosphamide, HD VP-16, or platinum-based chemotherapies (ICE, DHAP, or ESHAP) for chemomobilization. Although the patients in the VP-16 group (1.5 g/m^2) more frequently had advanced disease (stage IV) at the time of diagnosis and less frequently achieved a complete response before chemomobilization, the mobilization yield was significantly higher in the VP-16 group than in the other groups.

Patients treated with HD VP-16 showed a longer duration of neutropenia and a longer duration of G-CSF administration as well as a higher number of platelet transfusions. Moreover, the VP-16 group showed a higher incidence of neutropenic fever (67%) than the platinum-based chemotherapy group. However, we consider HD VP-16 a tolerable regimen for chemomobilization because no patient experienced severe infection or chemomobilization-related death and the incidence of neutropenic fever was similar to that in 2 previous studies of HD VP-16 (56% and 61%) [25,26]. In addition, there were no significant differences in median time to neutrophil engraftment and platelet engraftment according to chemomobilization regimen. tMDS/AML has emerged as a serious complication of HD VP-16 but remains controversial [9,27]. Krishnan et al. [27] reported that patients who received HD VP-16 (2.0 g/m^2) for PBSC mobilization were at a 12.3-fold increased risk of developing therapy-related AML with 11q23/21q22 abnormalities. However, a large recent cohort study reported that tMDS/AML occurred in 2% of patients receiving HD VP-16 (2.0 g/m^2) and in 4% of patients receiving G-CSF alone ($P = .62$), and the estimated incidence of tMDS/AML at 5 years was 2% in the HD VP-16 group and 2.6% in the G-CSF alone group [9]. In the present study, no patient developed tMDS/AML at a median follow-up of 26 months after HD VP-16 chemotherapy (1.5 g/m^2). Because studies with an intermediate dose of VP-16 for chemomobilization also showed a high mobilization yield and a relatively low incidence of toxicities [11,24], further clinical trials are needed to determine an appropriate dosage of VP-16 for chemomobilization.

Table 5
Toxicities According to Mobilization Regimen

	HD CTX (n = 31)	HD VP-16 (n = 29)	Platinum-Based Chemotherapy (n = 43)	*P*
Day of neutrophil nadir	10 (5-13)	10 (7-12)	12 (8-17)	<.001
Absolute neutrophil count at nadir ($\times 10^9$/L)	6 (0-470)	17 (0-50)	206 (0-2010)	<.001
Duration of ANC $<.5 \times 10^9$/L, days	5 (1-9)	7 (4-14)	2 (0-7)	<.001
Duration of G-CSF administration, days	8 (2-19)	14 (10-19)	7 (3-16)	<.001
Day of platelet nadir	12 (7-17)	12 (8-14)	13 (9-16)	.061
Platelet count at nadir ($\times 10^9$/L)	37 (18-171)	23 (7-70)	33 (10-242)	.010
Number of platelet transfusions	2 (0-20)	4 (1-10)	3 (0-20)	.036
Treatment-related mortality	0	0	0	
Neutropenic fever, number (%)	18 (58%)	14 (67%)	5 (12%)	<.001
Grade 4 infection	0	0	0	
tMDS/AML	0	0	0	

Table 6
Transplantation and Survival Outcomes

	HD CTX (n = 27)	HD VP-16 (n = 28)	Platinum-Based Chemotherapy (n = 40)	*P*
Conditioning regimen				<.001
Busulfan/thiotepa	0	14	6	
Busulfan/cytarabine/etoposide/melphalan	1	12	8	
Busulfan/cyclophosphamide/etoposide	16	1	13	
Busulfan/melphalan/etoposide	9	0	5	
Others	1	1	8	
$CD34^+$ cells infused ($\times 10^6$/kg)	4.88 (1.45-20.91)	9.15 (4.42-75.73)	5.77 (1.87-22.96)	<.001
Days to neutrophil engraftment	10 (6-23)	10 (9-12)	10 (6-29)	.105
Days to platelet engraftment	11 (4-42)	10 (7-22)	12 (4-50)	.272
2-Year PFS rate after ASCT	72%	81%	69%	.263
2-Year OS rate after ASCT	87%	84%	79%	.496

PFS indicates progression-free survival; OS, overall survival.

This study has several limitations. Because the peripheral blood $CD34^+$ cell count on the first day of apheresis was only available for 34% of patients, we could not include peripheral blood $CD34^+$ cell count when evaluating predictors of successful mobilization in this study. However, it did not really matter because we already had sufficient evidence that peripheral blood $CD34^+$ cell count on the first day of apheresis is a good predictor of PBSC mobilization yield [16,19,28]. In addition, the selection of chemomobilization regimen and the criteria for starting or stopping apheresis were determined according to each institution's policy. However, we consider our results to be reliable for selecting an effective chemomobilization regimen because the clinical characteristics that might affect the PBSC mobilization yield were comparable among the chemomobilization regimens and all apheresis procedures were usually performed according to similar guidelines in Korea.

In conclusion, the mobilization yield was significantly influenced by the chemomobilization regimen, and HD VP-16 increased PBSC mobilization and reduced the number of days of apheresis for successful mobilization in patients with NHL who had previously only been treated with CHOP or R-CHOP chemotherapy. These results could help guide chemomobilization regimen selection for patients with NHL who are being prepared for PBSC mobilization.

ACKNOWLEDGMENTS

Financial disclosure: There are no financial supports to report.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: J. S. K. was the principal investigator. S. Y. H. and J. S. K. designed the study, analyzed the data, and wrote the article. J.-W. C., S.-J. K., Y. H. M., D.-H. Y., J.-S. A., W.-S. L., H.-M. R., Y. R. D., H. S. L., J. H. L., S. Y. O., C. S., and H.-Y. Y. treated the patients, collected the clinical data, and revised the article.

REFERENCES

1. Gordan LN, Sugrue MW, Lynch JW, et al. Poor mobilization of peripheral blood stem cells is a risk factor for worse outcome in lymphoma patients undergoing autologous stem cell transplantation. *Leuk Lymphoma*. 2003;44:815-820.
2. Milpied N, Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. *N Engl J Med*. 2004;350:1287-1295.
3. Rosenfeld CS, Shadduck RK, Zeigler ZR, et al. Cyclophosphamide-mobilized peripheral blood stem cells in patient with lymphoid malignancies. *Bone Marrow Transplant*. 1995;15:433-438.
4. Pavone V, Gaudio F, Guarini A, et al. Mobilization of peripheral blood stem cells with high-dose cyclophosphamide or the DHAP regimen plus G-CSF in non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2002;29:285-290.
5. Watts MJ, Ings SJ, Leverett D, et al. ESHAP and G-CSF is a superior blood stem cell mobilizing regimen compared to cyclophosphamide 1.5 g m(-2) and G-CSF for pre-treated lymphoma patients: a matched pairs analysis of 78 patients. *Br J Cancer*. 2000;82:278-282.
6. Lee JL, Kim S, Kim SW, et al. ESHAP plus G-CSF as an effective peripheral blood progenitor cell mobilization regimen in pretreated non-Hodgkin's lymphoma: comparison with high-dose cyclophosphamide plus G-CSF. *Bone Marrow Transplant*. 2005;35:449-454.
7. Moskowitz CH, Bertino JR, Glassman JR, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 1999;17:3776-3785.
8. Copelan EA, Ceselski SK, Ezzone SA, et al. Mobilization of peripheral-blood progenitor cells with high-dose etoposide and granulocyte colony-stimulating factor in patients with breast cancer, non-Hodgkin's lymphoma, and Hodgkin's disease. *J Clin Oncol*. 1997;15:759-765.
9. Mahindra A, Bolwell BJ, Rybicki L, et al. Etoposide plus G-CSF priming compared with G-CSF alone in patients with lymphoma improves mobilization without an increased risk of secondary myelodysplasia and leukemia. *Bone Marrow Transplant*. 2012;47:231-235.
10. Wood WA, Whitley J, Moore D, et al. Chemomobilization with etoposide is highly effective in patients with multiple myeloma and overcomes the effects of age and prior therapy. *Biol Blood Marrow Transplant*. 2011;17:141-146.
11. Wood WA, Whitley J, Goyal R, et al. Effectiveness of etoposide chemomobilization in lymphoma patients undergoing auto-SCT. *Bone Marrow Transplant*. 2012;48:771-776.
12. Nowrousian MR, Waschke S, Bojko P, et al. Impact of chemotherapy regimen and hematopoietic growth factor on mobilization and collection of peripheral blood stem cells in cancer patients. *Ann Oncol*. 2003;14(Suppl. 1):i29-i36.
13. Ford CD, Green W, Warenski S, Petersen FB. Effect of prior chemotherapy on hematopoietic stem cell mobilization. *Bone Marrow Transplant*. 2004;33:901-905.
14. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. Accessed May 20, 2013.
15. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579-586.
16. Ozkurt ZN, Yegin ZA, Suyani E, et al. Factors affecting stem cell mobilization for autologous hematopoietic stem cell transplantation. *J Clin Apher*. 2010;25:280-286.
17. Kuittinen T, Nousiainen T, Halonen P, et al. Prediction of mobilisation failure in patients with non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2004;33:907-912.
18. Hosing C, Saliba RM, Ahlawat S, et al. Poor hematopoietic stem cell mobilizers: a single institution study of incidence and risk factors in patients with recurrent or relapsed lymphoma. *Am J Hematol*. 2009;84:335-337.
19. Gertz MA. Current status of stem cell mobilization. *Br J Haematol*. 2010;150:647-662.
20. Wuchter P, Ran D, Bruckner T, et al. Poor mobilization of hematopoietic stem cells-definitions, incidence, risk factors, and impact on outcome of autologous transplantation. *Biol Blood Marrow Transplant*. 2010;16:490-499.
21. Ketterer N, Salles G, Moullet I, et al. Factors associated with successful mobilization of peripheral blood progenitor cells in 200 patients with lymphoid malignancies. *Br J Haematol*. 1998;103:235-242.
22. Sheppard D, Bredeson C, Allan D, Tay J. Systematic review of randomized controlled trials of hematopoietic stem cell mobilization strategies for autologous transplantation for hematologic malignancies. *Biol Blood Marrow Transplant*. 2012;18:1191-1203.

23. Milone G, Leotta S, Indelicato F, et al. G-CSF alone vs cyclophosphamide plus G-CSF in PBPC mobilization of patients with lymphoma: results depend on degree of previous pretreatment. *Bone Marrow Transplant*. 2003;31:747-754.
24. Milone G, Leotta S, Battiato K, et al. Intermediate dose etoposide plus G-CSF 16 g/kg is more effective than cyclophosphamide 4 g/m(2) plus G-CSF 10 g/kg in PBSC mobilization of lymphoma patients. *Leuk Lymph*. 2007;48:1950-1960.
25. Reiser M, Josting A, Draube A, et al. Successful peripheral blood stem cell mobilization with etoposide (VP-16) in patients with relapsed or resistant lymphoma who failed cyclophosphamide mobilization. *Bone Marrow Transplant*. 1999;23:1223-1228.
26. Li B, Yang JL, Shi YK, et al. Etoposide 1.0 g/m2 or 1.5 g/m2 combined with granulocyte colony-stimulating factor for mobilization of peripheral blood stem cells in patients with malignancy: efficacy and toxicity. *Cytotherapy*. 2009;11:362-371.
27. Krishnan A, Bhatia S, Slovak ML, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. *Blood*. 2000;95:1588-1593.
28. Pusic I, Jiang SY, Landua S, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. *Biol Blood Marrow Transplant*. 2008;14:1045-1056.