

## ORIGINAL ARTICLE

# Multicenter study of intravenous busulfan, cyclophosphamide, and etoposide (i.v. Bu/Cy/E) as conditioning regimen for autologous stem cell transplantation in patients with non-Hodgkin's lymphoma

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The current study aimed to evaluate the efficacy and toxicity of a combination of intravenous busulfan, cyclophosphamide and etoposide (i.v. Bu/Cy/E) as a conditioning regimen prior to autologous hematopoietic stem cell transplantation in patients with non-Hodgkin's lymphoma (NHL). Sixty-four patients with relapsed/refractory ( $n = 36$ ) or high-risk ( $n = 28$ ) lymphoma were enrolled. The high-dose chemotherapy consisted of i.v. Bu ( $0.8 \text{ mg kg}^{-1}$  i.v. q 6 h from day  $-7$  to day  $-5$ ), Cy ( $50 \text{ mg kg}^{-1}$  i.v. on day  $-3$  and day  $-2$ ) and E ( $400 \text{ mg m}^{-2}$  i.v. on day  $-5$  and day  $-4$ ). The median age was 43 (range 18–65) years, and 39 patients were male. Diffuse large B-cell lymphoma (40.6%) was the most common histological subtype. All evaluable patients achieved an engraftment of neutrophils (median, day 12) and platelets (median, day 13). Hepatic veno-occlusive disease was observed in four patients (three mild, one moderate grade), and two patients (3.1%) died from treatment-related complications. At a median follow-up of 16.4 months, 15 patients (23.4%) exhibited a relapse or progression, while 13 patients (20.3%) had died of disease. The estimated 3-year overall and progression-free survival for all patients was 72.1 and 70.1%, respectively. In conclusion, the conditioning regimen of i.v. Bu/Cy/E was well tolerated and seemed to be effective in patients with aggressive NHL.

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## Introduction

High-dose chemotherapy followed by autologous stem cell rescue is the current standard of care after primary-therapy failure for patients with aggressive non-Hodgkin's lymphoma (NHL).<sup>1</sup> Studies conducted in the 1980s demonstrated that patients with at least partial remission of a relapsed disease after submyeloablative chemotherapy have a 35–50% long-term survival rate with various conditioning regimens.<sup>2–6</sup> In a landmark randomized trial,<sup>3</sup> patients with a sensitive relapse achieved a 53% long-term survival with high-dose chemotherapy versus a 32% long-term survival with continued nonmyeloablative chemotherapy ( $P = 0.038$ ). Furthermore, autologous stem cell transplantation (ASCT) as a consolidation treatment has exhibited superior survival compared to conventional chemotherapy for young patients with high-risk NHL in several clinical trials.<sup>7,8</sup>

While carmustine (BCNU) and total body irradiation-based regimens are commonly used, the relative effectiveness of different preparative regimens has been difficult to determine, as most previous studies have been small with few meaningful comparisons between regimens. Busulfan (Bu)-based preparative regimens, which are commonly used with allogeneic SCT,<sup>9</sup> have also been studied with ASCT for lymphomas.<sup>10,11</sup> As a result, several studies have reported a long-term survival of 45% after ASCT for patients with aggressive NHL when using a busulfan/cyclophosphamide/etoposide (Bu/Cy/E) preparative, previously developed for allogeneic SCT.<sup>10–12</sup> However, the difficulty in predicting and assessing the dose delivered with

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the oral administration of high-dose Bu in preparative regimens for SCT results in a significant risk of lethal pulmonary or hepatic toxicity due to inadvertent overdosing,<sup>13</sup> or else the potential of graft failure<sup>14</sup> or a persistent malignant disease after transplantation due to under-dosing.<sup>15</sup>

After the introduction of a parenteral formula of Bu, several studies have noted that i.v. Bu as part of a preparative regimen is effective and can reduce veno-occlusive disease (VOD) and early treatment mortality with allogeneic hematopoietic SCT.<sup>16–18</sup> However, very few studies have focused on the effectiveness and safety of i.v. Bu in an ASCT setting. Accordingly, the current study attempted to evaluate the efficacy and toxicity of the combination of i.v. Bu, Cy and E as a conditioning regimen prior to ASCT in patients with NHL.

## Materials and methods

### Patient enrollment

Patients with a high-intermediate/high-risk international prognostic index at diagnosis or with salvage chemotherapy-sensitive relapse/refractory NHL were considered eligible for ASCT. Other inclusion criteria were age  $\leq 65$  years; Eastern Cooperative Oncology Group performance status  $\leq 2$ ; and normal cardiac, pulmonary, renal and hepatic function tests. All patients gave informed consent for high-dose chemotherapy followed by ASCT and written consent for the use of their records for research.

### Hematopoietic stem cell mobilization and collection

All patients underwent transplantation with peripheral blood hematopoietic stem cells mobilized with a granulocyte colony-stimulating factor alone ( $n=24$ , 37.5%) or chemotherapy plus the granulocyte colony-stimulating factor ( $n=40$ , 62.5%). The hematopoietic stem cells were collected from all patients using high-volume leukapheresis through a large-bore central venous catheter, with a target of more than  $2 \times 10^6 \text{ kg}^{-1}$  of CD34+ cells.

### Conditioning regimen

The conditioning regimen before the ASCT consisted of i.v. Bu (Busulfex, Jeil-Kirin Pharm Inc., Seoul, Korea;  $0.8 \text{ mg kg}^{-1}$  i.v. q 6 h from day  $-7$  to day  $-5$ ), Cy ( $50 \text{ mg kg}^{-1}$  i.v. on day  $-3$  and day  $-2$ ) and E ( $400 \text{ mg m}^{-2}$  i.v. on day  $-5$  and day  $-4$ ). The hematopoietic stem cells were infused on day 0. The Busulfex infusions were admixed as per the package insert guidelines to a final concentration of  $0.54 \text{ mg ml}^{-1}$ . The chemotherapy doses were based on the actual body weight or ideal body weight, whichever was less; however, if the actual body weight exceeded the ideal body weight by 20%, then the ideal body weight + 10% was used for the dosage calculations.

### Supportive care

All patients received a seizure prophylaxis with phenytoin at a dose of 1 g per os (load) on day 1 prior to the first dose of Bu, followed by 300 mg per os daily for 4 days. The serum phenytoin levels were not monitored. The uroepithe-

lial prophylaxis for Cy administration consisted of hyperhydration and mesna. The granulocyte colony-stimulating factor was given daily at a dose of  $5 \mu\text{g kg}^{-1}$  following the transplantation until the neutrophil count reached  $5 \times 10^9 \text{ l}^{-1}$ . The antiemetics, blood component, antibacterial and antifungal antibiotics, and other supportive care measures were all used according to the respective guidelines at each institution.

### Definition and evaluation criteria

The day of the stem cell infusion was defined as day 0. Myeloid engraftment was defined as the first day of 3 consecutive days when the absolute neutrophil count was  $\geq 0.5 \times 10^9 \text{ l}^{-1}$ , while platelet engraftment was defined as the time taken to achieve platelets  $\geq 20 \times 10^9 \text{ l}^{-1}$  without requiring a transfusion. The patient response was evaluated 1 month after the transplantation and thereafter every 3 months during the follow-up according to the NHL response criteria,<sup>19</sup> plus the toxicity was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 grading system. Cytomegalovirus antigenemia was also monitored after transplantation, and hepatic VOD defined according to the clinical criteria devised by McDonald *et al.*<sup>20</sup>

### Statistical analysis

The principal end points in the present study included overall survival (OS) and progression-free survival (PFS). OS was measured from the transplantation day until the date of death or last follow-up, while PFS was calculated from the transplantation day until disease progression, relapse or death from any cause. The survival curves were plotted using the Kaplan–Meier method, and the statistical data obtained using an SPSS software package (SPSS 11.0 Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Sixty-four patients with aggressive NHL were enrolled between May 2004 and September 2006 at eight medical centers in Korea, and the patient characteristics are summarized in Table 1. The median age was 43 (range 18–65) years, and 39 patients were male. Diffuse large B-cell lymphoma (40.6%) was the most common histological subtype. Thirty-four patients (53.1%) were classified as high intermediate or high risk according to the international prognostic index scoring system at the time of diagnosis. Thirty-eight patients (59.4%) had received at least two chemotherapy regimens before transplantation, while 36 patients (56.2%) had a relapsed or refractory disease at the time of transplantation.

### Engraftment, toxicity and transplant-related mortality

The engraftment and toxicity results are summarized in Table 2. The median dose of CD34+ and mononuclear cells transplanted was  $6.0 \times 10^6$  and  $8.2 \times 10^8 \text{ kg}^{-1}$ , respectively. Since two patients died before day 30, 62 patients were evaluated for hematopoietic recovery. All evaluable

**Table 1** Patient characteristics

Characteristic	Number of patients (n = 64, %)
<i>Age (years)</i>	
Median (range)	43 (18–65)
<i>Gender</i>	
Male	39 (60.9)
Female	25 (39.1)
<i>ECOG performance status at transplant</i>	
0–1	51 (79.7)
2	13 (20.3)
<i>Histologic subtype</i>	
Diffuse large B cell	26 (40.6)
Peripheral T cells, unspecified	12 (18.8)
Extranodal NK/T cells, nasal type	9 (14.1)
Anaplastic large cells	6 (9.4)
Angioimmunoblastic T cells	3 (4.7)
Others	8 (12.5)
<i>International prognostic index at diagnosis</i>	
Low	12 (18.8)
Low-intermediate	18 (28.1)
High-intermediate	26 (40.6)
High	8 (12.5)
<i>Number of prior chemotherapy regimens</i>	
1	26 (40.6)
2	27 (42.2)
≥3	11 (17.2)
<i>Status at transplantation</i>	
High risk in remission	28 (43.8)
Relapsed or refractory	36 (56.2)
<i>Response status at transplantation</i>	
In complete remission	39 (60.9)
In partial remission	25 (39.1)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

patients achieved an engraftment of neutrophils (median, day 12) and platelets (median, day 13), although the platelet engraftment was delayed in the case of three patients (days 62, 106 and 139). The most common non-hematologic toxicity was mucositis, which occurred with a grade 1/2 intensity in 36 patients (56.3%). Hepatic VOD was observed in four patients (three mild and one moderate grade), plus one patient required treatment. Although bacteremia was documented in eight patients (12.5%), all were successfully treated with antibiotics. One patient with refractory peripheral T-cell lymphoma, who received alemtuzumab and cytotoxic chemotherapy as a salvage treatment, developed cytomegalovirus retinitis after transplantation. Two patients (3.1%) died within 30 days of transplantation from treatment-related complications. One patient died from bleeding and another from sudden cardiogenic shock.

#### Response and survival

Fifty-one patients (79.7%) achieved a complete response 1 month after ASCT, while two patients showed progressive disease. Among 25 patients with NHL in a partial response

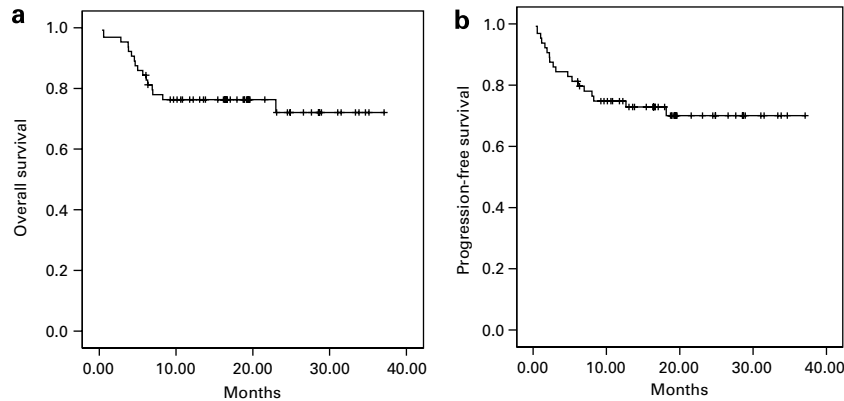
**Table 2** Transplantation outcome and toxicity

Characteristic	Number of patients (n = 64, %)
<i>Transplanted cell dose</i>	
CD34+ cells ( $\times 10^6 \text{ kg}^{-1}$ )	Median 6.0 (range 2.1–19.2)
Mononuclear cells ( $\times 10^8 \text{ kg}^{-1}$ )	Median 8.2 (range 1.5–17.7)
<i>Engraftment days</i>	
Neutrophils	Median 12 (range 8–48)
Platelets	Median 13 (range 7–263)
<i>Response after transplantation</i>	
Complete remission	51 (79.7)
Partial remission	8 (12.5)
Stable disease	1 (1.6)
Progressive disease	2 (3.1)
<i>Infectious complication</i>	
Fever without documented bacteremia	41 (64.1)
Documented bacteremia	8 (12.5)
<i>Veno-occlusive disease</i>	
Mild	3 (4.7)
Moderate	1 (1.6)
<i>Cytomegalovirus infection</i>	
Antigenemia	1 (1.6)
Disease (retinitis)	1 (1.6)
Progression or relapse	15 (23.4)
<i>Death</i>	
Treatment-related mortality	2 (3.1)
Disease-related death	14 (21.9)

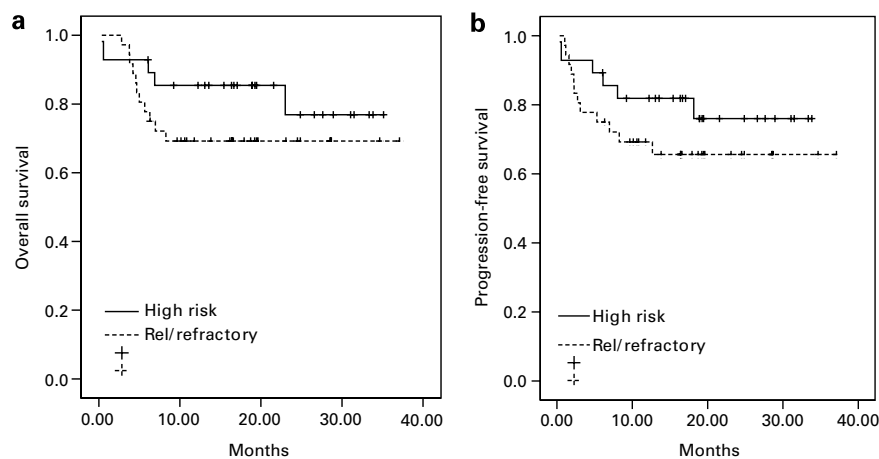
at transplantation, 12 patients (48.0%) converted partial response to a complete response after transplantation. At a median follow-up of 16.4 months (range 0.4–37.1), 15 patients (23.4%) exhibited a relapse or progression, while 13 patients (20.3%) had died of disease. The estimated 3-year OS and PFS for all patients was  $72.1 \pm 6.5$  and  $70.1 \pm 6.1\%$ , respectively (Figure 1). The survival of the patients with high-risk NHL showed a superior trend to that of the patients with relapsed or refractory NHL (estimated 3-year OS;  $76.9 \pm 10.1$  versus  $69.2 \pm 7.7\%$ ,  $P$ -value = 0.2386; estimated 3-year PFS;  $76.0 \pm 8.8$  versus  $65.6 \pm 8.1\%$ ,  $P$ -value = 0.2721) (Figure 2), while the survivals between the B-cell NHL and T-cell NHL were not different (estimated 3-year OS;  $70.2 \pm 9.9$  versus  $74.5 \pm 7.8\%$ ). In the multivariate analysis, including sex, age, pathologic subtype and status at transplantation, no statistically significant factor was observed (data not shown).

#### Discussion

In the current study, the combination chemotherapy of i.v. Bu/Cy/E as a conditioning regimen prior to ASCT produced active antitumor activity and a safe toxicity profile in patients with aggressive NHL. The estimated 3-year OS of 69.2% for the patients with relapsed/refractory NHL and 76.9% for the patients with high-risk NHL following treatment with the study regimen were comparable to previous results reported for other



**Figure 1** Overall (a) and progression-free survival (b) curves for all patients.



**Figure 2** Overall (a) and progression-free survival (b) curves according to status at transplantation ( $P$ -value = not significant).

conditioning regimens, although the median follow-up was short in the current study.<sup>3–8</sup> For example, the commonly used conditioning regimen of BCNU, etoposide, cytarabine, cyclophosphamide and mesna demonstrated a 5-year OS of 53% for patients with chemotherapy-sensitive NHL in relapse in a randomized trial.<sup>3</sup> Meanwhile, Gulati *et al.*<sup>5</sup> reported that a hyperfractionated total body irradiation, E and Cy combination regimen produced a long-term disease-free survival of 57% in patients with refractory and resistant NHL. However, a recent report by Bhatia *et al.*<sup>21</sup> for the Bone Marrow Transplant Survivor Study documented a significantly increased late nonrelapse mortality after ASCT for hematologic malignancies with BCNU-based regimens that was not observed with Bu- or total body irradiation-based regimens, thereby supporting the search for safer and equally effective preparative regimens.

Since Bu-based conditioning regimens have been extensively utilized in autologous and allogeneic SCT for a variety of lymphohematopoietic disorders, several studies have also been performed for NHL.<sup>10–12,22</sup> Copelan *et al.*<sup>10</sup> reported that oral Bu (14 mg kg<sup>-1</sup>)/Cy (120 mg kg<sup>-1</sup>)/E (50 or 60 mg kg<sup>-1</sup>) as a preparative regimen with ASCT achieved a 3-year PFS of 46.9% in 382 patients with

relapsed or refractory NHL, and suggested that the results for the Bu/Cy/E regimen were superior to those for their previous regimen of Bu (16 mg kg<sup>-1</sup>)/Cy (120 mg kg<sup>-1</sup>), and exhibited a low incidence of transplant-related mortality or secondary complications of myelodysplasia and acute myeloid leukemia. Hanel *et al.*<sup>11</sup> also reported that an oral Bu (16 mg kg<sup>-1</sup>)/Cy (120 mg kg<sup>-1</sup>)/E (30 or 45 mg kg<sup>-1</sup>) regimen was effective (3-year OS, 63%) and well tolerated in 53 patients with Hodgkin's disease or NHL. However, a relative high incidence (2.9–5.8%) of severe VOD, which is life threatening, was also observed in their studies. Furthermore, since the pharmacokinetic profile of orally administered Bu demonstrates wide interpatient and inpatient variability due to age-related differences, alterations in absorption, circadian variations and drug–drug interactions, the oral administration of high-dose Bu for SCT can cause a significant risk of hepatic toxicity.<sup>23–25</sup>

Although attempts to develop an i.v. preparation of Bu were initially limited due to the drug's poor aqueous solubility, several formulations have since been investigated, including a formulation that uses dimethyl acetamide and polyethylene glycol (i.v. Busulfex). After the introduction of i.v. Bu, several studies have demonstrated a lower incidence rate of VOD with a Bu/Cy preparative

regimen due to its dose assurance with predictable pharmacokinetics.<sup>16,17</sup> A recent historically controlled study by Aggarwal *et al.*<sup>26</sup> also reported that the substitution of i.v. Bu for oral Bu in a Bu/Cy/E conditioning regimen improved the outcomes for patients with intermediate- and high-risk aggressive NHL who underwent ASCT, with the suggestion that this was primarily due to a decreased Bu-associated regimen-related mortality. In the present study, as the total dose of i.v. Bu was reduced (0.8 mg kg<sup>-1</sup> every 6 h for 3 days), only one patient (1.6%) experienced moderate VOD, while two patients (3.1%) died from treatment-related mortality.

In conclusion, a conditioning regimen of i.v. Bu/Cy/E was found to be well tolerated and seemed to be effective in patients with aggressive NHL. Accordingly, this regimen can be regarded as an important treatment option for ASCT in the case of NHL.

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