

Yttrium-90 ibritumomab tiuxetan plus busulfan, cyclophosphamide, and etoposide (BuCyE) versus BuCyE alone as a conditioning regimen for non-Hodgkin lymphoma

Jae-Cheol Jo¹, Dok Hyun Yoon¹, Shin Kim¹, Jung Sun Park¹, Chan-Sik Park², Jooryung Huh², Sang-Wook Lee³, Jin-Sook Ryu⁴, Cheolwon Suh¹

Departments of ¹Oncology, ²Pathology, ³Radiation Oncology, and ⁴Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Correspondence to
 Cheolwon Suh, M.D., Ph.D.
 Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea
 Tel: +82-2-3010-3209
 Fax: +82-2-3010-6961
 E-mail: csuh@amc.seoul.kr

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Background

Radioimmunotherapy agents have a highly significant role in autologous stem cell transplantation as they improve tolerability and increase the efficacy of the conditioning regimen.

Methods

We retrospectively analyzed the efficacy and toxicity of yttrium-90 ibritumomab tiuxetan (Zevalin) combined with intravenous busulfan, cyclophosphamide, and etoposide (Z-BuCyE) compared with those of BuCyE alone followed by autologous stem cell transplantation in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (NHL). The efficacy, toxicity, and engraftment characteristics were compared between 19 patients who received Z-BuCyE and 19 historical controls who received BuCyE.

Results

The 2 treatment groups shared similar baseline characteristics. The median time to platelet engraftment ($>20 \times 10^9/L$) and neutrophil engraftment ($>0.5 \times 10^9/L$) did not significantly differ between the Z-BuCyE group (12 days and 10 days, respectively) and the BuCyE group (12 days and 10 days, respectively). No significant differences were observed between the groups with respect to toxicities and treatment-related mortality. The median follow-up period was 30.4 months, and median event-free survival was generally better in the Z-BuCyE group (12.5 months) vs. the BuCyE group (6.2 months, $P=0.236$). No significant difference in overall survival between the groups was noted.

Conclusion

Adding ibritumomab tiuxetan to BuCyE high-dose chemotherapy may benefit patients with relapsed or refractory B-cell NHL with no risk of additional toxicity.

Key Words Yttrium-90 ibritumomab tiuxetan, BuCyE, Autologous stem cell transplantation, Non-Hodgkin lymphoma

INTRODUCTION

High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is considered standard therapy for patients with chemo-sensitive relapsed aggressive lymphoma. The PARMA trial demonstrated that the 5-year event-free survival rate was superior in patients who received ASCT compared with those undergoing conventional chemotherapy [1]. Other randomized trials have also shown im-

proved event-free survival [2, 3]. However, despite treatment with an intensified chemotherapy regimen combined with ASCT, long-term disease control rates range from only 25-45% in patients with relapsed or refractory aggressive lymphomas [4-6]. Relapses in patients receiving HDC in conjunction with ASCT are primarily caused by cancer cells remaining in the body after ablative chemotherapy [7]. Therefore, approaches involving methods for improving eradication of lymphoma cells and preventing recurrence are urgently needed for improving survival after ASCT.

Investigators have recently incorporated radioimmunotherapies (RIT) with agents such as yttrium-90 ibritumomab tiuxetan (Zevalin), a radiotherapeutic monoclonal antibody directed against B-lymphocyte antigen CD20, into conditioning regimens for treating relapsed lymphoma [8-10]. Studies have shown that the combination of ibritumomab tiuxetan with BEAM (carmustine [BCNU], etoposide, cytosine arabinoside, and melphalan) or Zevalin (Z)-BEAM showed promising results. Particularly, improved survival outcomes associated with ibritumomab tiuxetan in combination with HDC for patients with aggressive lymphomas were noted in comparison with those for historical controls without the use of RIT [9-11]. Several lines of evidence suggested that the inclusion of ibritumomab tiuxetan in Z-BEAM compared with BEAM alone administered prior to ASCT can improve survival outcomes [12, 13].

Busulfan (Bu)-based conditioning regimens, which are commonly used prior to allogeneic SCT, have also been used with ASCT for treating lymphoma [14-16]. Comparative analysis showed that busulfan, cyclophosphamide and etoposide (BuCyE) together are an effective conditioning regimen for ASCT, showing similar survival outcomes and toxicity profiles as BEAM [17]. To combine a BuCyE conditioning regimen with RIT, we previously demonstrated the efficacy and safety of ibritumomab tiuxetan combined with BuCyE (Z-BuCyE) followed by ASCT in patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NHL) [18]. Although the role of ibritumomab tiuxetan in conditioning regimens has been assumed, limited information exists regarding the comparative efficacies and toxicities of this regimen and BuCyE alone. We therefore compared the efficacy and toxicity of the Z-BuCyE and BuCyE regimens in patients with NHL.

MATERIALS AND METHODS

1. Patients

Between October 2005 and May 2011, 71 NHL patients underwent HDC using BuCyE (N=52) or Z-BuCyE (N=19), followed by ASCT, at Asan Medical Center (Seoul, Korea). Patients treated with Z-BuCyE had histologically confirmed, relapsed, or refractory CD20 positive B-cell NHL, including follicular, marginal zone B-cell, mantle cell, diffuse large B-cell, and Burkitt lymphomas. Fifteen patients treated in a prospective multicenter trial with Z-BuCyE were included in the analysis and were included in the Z-BuCyE group [18]. Of 52 patients receiving BuCyE, 19 patients presented with B-cell NHL histology. This group of patients comprised the historical controls for the Z-BuCyE group (N=19). Other patients presented with primary central nervous system lymphoma (N=18), natural killer T-cell lymphoma (N=6), and peripheral T-cell NHL (N=9).

2. Transplant procedure and supportive care

Chemotherapy doses were based on body weight as follows. Patients in the Z-BuCyE group received a Z-BuCyE

conditioning regimen, which corresponded to rituximab 250 mg/m² on day -21 and day -14, ibritumomab tiuxetan 0.4 mCi/kg on day -14, busulfan 3.2 mg/kg on days -7 through -5, cyclophosphamide 50 mg/kg on days -3 and -2, and etoposide 400 mg/m² on days -5 and -4. Patients in the BuCyE group were given the same regimen as above, excluding rituximab and ibritumomab tiuxetan. Hematopoietic SCs were then infused on day 0.

All patients were administered seizure prophylaxis with phenytoin prior to the first dose of busulfan. The uroepithelial prophylaxis for cyclophosphamide administration included hydration and mesna to prevent bleeding from the bladder. All patients received subcutaneous granulocyte colony-stimulating factor (G-CSF) (5 g/kg) beginning on day 1 of ASCT until neutrophil counts were stable at $>1.0 \times 10^9/L$ for 3 consecutive days. Prophylaxis for opportunistic infections and antimicrobial therapy in the case of febrile episodes were administered according to previously described protocols [17-19].

3. Definitions and response evaluation

In this study, indolent lymphoma indicated the presence of follicular and marginal zone B-cell lymphomas, while aggressive lymphoma indicated the presence of mantle cell, diffuse large B-cell, and Burkitt lymphomas. The period of event-free survival (EFS) was defined as the time from the day of ASCT to the time of disease progression, relapse, or death from any cause. Overall survival (OS) was defined as the time from the day of ASCT to the time of death from any cause. Response was evaluated according to the response criteria provided by the International Working Group [20]. The duration of complete response (CR) was defined as the time from the day of ASCT to the time of relapse in patients with continued CR, or from the day of achievement of CR after ASCT to the time of relapse in patients with induced CR. As noted above, the day of SC infusion was defined as day 0. Chemo-sensitive disease was defined as a reduction in measurable disease following salvage chemotherapy prior to ASCT, meeting the criteria of partial response (PR). Patients were considered to have chemo-resistant disease if the reduction in measurable disease did not meet the PR criteria. Time to neutrophil engraftment was defined as the time from the day of ASCT to the first day of the 3 consecutive days when the absolute neutrophil count (ANC) was $>0.5 \times 10^9/L$, and the time to platelet engraftment was defined as the time from the day of ASCT to the first day when the platelet count was $>20 \times 10^9/L$. Toxicities were assessed and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), version 3.0. Response evaluations were performed every 3 months after ASCT for the first 2 years, every 6 months for the next 3 years, and then annually or as clinically indicated.

4. Statistical analysis

Between-group comparisons were conducted using the Mann-Whitney *U*-test for continuous variables and the

chi-square test or Fisher exact test for categorical variables. Differences between Kaplan-Meier curves for EFS, OS, and CR durations were assessed using the log-rank test. Two-tailed *P* values < 0.05 were regarded as significant. All calculations were performed using the Statistical Package for the Social Sciences (SPSS), version 11.0, for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics

Baseline characteristics of the 38 patients included in this study are summarized in Table 1. The median age was 52 years (range, 29-65) in the BuCyE group and 54 years (range, 27-64) in Z-BuCyE group. Of these patients, 15 patients in the BuCyE group and 17 patients in the Z-BuCyE group had an aggressive histology. The numbers of patients with >2 prior chemotherapy regimens were 6 and 4 in the BuCyE

and Z-BuCyE groups, respectively. Most patients (N=36) received the ESHAP regimen (etoposide, carboplatin, cytarabine, and methylprednisolone) as pre-ASCT chemotherapy. A higher percentage of patients in the Z-BuCyE group were male. Other characteristics, including performance status, number of previous regimens of chemotherapy, prior radiotherapy, prior use of rituximab, involvement of extranodal sites, International Prognostic Index (IPI), and disease status at the time of salvage, were similar between the 2 groups.

2. Hematopoietic engraftment and toxicity

Engraftment data are summarized in Table 2. The median time to neutrophil and platelet engraftment did not differ significantly between the 2 groups. Thrombocytopenia persisted for 103 days after ASCT in one female patient who received Z-BuCyE. Bone marrow examination for this patient showed the presence of hypocellular marrow without lymphoma involvement. However, the patient had enlarged cervical lymph nodes at 9 months, indicating a relapse. The

Table 1. Patient characteristics.

	BuCyE (N=19)	Z-BuCyE (N=19)	<i>P</i>
Age at transplant, years (median)	52 (29-65)	54 (27-64)	0.969
Gender			0.023
Male	6 (31.6%)	13 (68.4%)	
Female	13 (68.4%)	6 (31.6%)	
Performance status at ASCT 0-1	19	19	
Histology			0.374
Indolent NHL (MZL, FL)	4 (21.1%)	2 (10.5%)	
Aggressive NHL (DLBCL, BL, MCL)	15 (78.9%)	17 (89.5%)	
Prior chemotherapy regimens			0.714
2	13 (68.4%)	15 (78.9%)	
3	6 (31.6%)	4 (21.1%)	
Prior radiotherapy	6 (31.6%)	2 (10.5%)	0.111
Previous use of rituximab	10 (52.6%)	12 (63.1%)	0.511
Extranodal sites ≥ 1 at ASCT	8 (42.1%)	6 (31.6%)	0.501
IPI at ASCT			0.946
Low	14 (73.7%)	13 (68.4%)	
Low-intermediate	3 (15.8%)	3 (15.8%)	
High-intermediate	1 (5.3%)	2 (10.5%)	
High	1 (5.3%)	1 (5.3%)	
Disease status at ASCT			0.892
CR	6 (31.6%)	8 (42.1%)	
Chemo-sensitive disease	11 (57.9%)	9 (47.4%)	
Chemo-resistant disease	2 (10.5%)	2 (10.5%)	

Abbreviations: ASCT, autologous stem cell transplantation; NHL, non-Hodgkin's lymphoma; MZL, marginal zone B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; IPI, international prognostic index; CR, complete response; Z-BuCyE, ibritumomab tiuxetan, busulfan, cyclophosphamide and etoposide.

Table 2. Hematopoietic engraftment after ASCT.

	BuCyE (N=19) median (range)	Z-BuCyE (N=19) median (range)	<i>P</i>
Time to neutrophils > 0.5 × 10 ⁹ /L (days)	10 (9-12)	10 (8-12)	0.422
Time to platelets > 20 × 10 ⁹ /L (days)	12 (8-35)	12 (3-103)	0.927
Transfused red blood cells (units)	4 (2-25)	4 (0-17)	0.200
Transfused platelets (times)	7 (2-50)	6 (2-30)	0.306
Hospitalization duration (days)	30 (16-93)	21 (14-84)	0.405

requirement for the transfusion of red blood cells and platelets and the median duration of hospitalization were comparable between the 2 groups.

Table 3 shows that the percentage of patients with mucositis, nausea, and diarrhea of at least grade 2 was generally higher in the Z-BuCyE group than in the BuCyE group, but this result was not statistically significant. Febrile neutropenia occurred in 73.7% and 94.7% of patients conditioned

with BuCyE and Z-BuCyE, respectively ($P=0.180$). One patient in the Z-BuCyE group experienced septicemia caused by *Klebsiella pneumoniae*, but improved following treatment with antibiotics. Another patient in the Z-BuCyE group and 2 in the BuCyE group died within 100 days after ASCT due to treatment-related complications. One patient died due to veno-occlusive disease (VOD) after Z-BuCyE, and 2 patients died due to bacterial infections accompanied by severe mucositis after BuCyE.

Table 3. Toxicities associated with conditioning regimens.

	BuCyE (N=19)	Z-BuCyE (N=19)	P
Mucositis ^{a)}	6 (31.6%)	8 (42.1%)	0.501
Nausea ^{a)}	8 (42.1%)	11 (57.9%)	0.330
Vomiting ^{a)}	2 (10.5%)	1 (5.3%)	NC ^{b)}
Diarrhea ^{a)}	5 (26.3%)	6 (31.6%)	0.721
Febrile neutropenia	14 (73.7%)	18 (94.7%)	0.180
Septicemia	0	1 (5.3%)	NC ^{b)}
Veno-occlusive disease	0	1 (5.3%)	NC ^{b)}
Treatment-related mortality	2 (10.5%)	1 (5.3%)	NC ^{b)}

^{a)}Toxicities of grade 2 or higher, ^{b)}NC: not calculated due to the small number of events.

3. Response and survival outcomes

The objective overall response rate was 89.5% (17/19) in the Z-BuCyE group and 78.9% (15/19) in the BuCyE group ($P=0.649$). CR rates in the Z-BuCyE and BuCyE groups were 78.9% (continued CR, 100% [8/8]; induced CR, 63.6% [7/11]) and 73.7% (continued CR, 83.3% [5/6]; induced CR, 69.2% [9/13]), respectively ($P=1.000$). Median follow-up duration for survivors was 30.4 months (range, 0.8-68.5 months). There was a trend toward improved EFS in the Z-BuCyE group, with a 3-year EFS rate of 26.8% compared with that of 15.8% in the BuCyE group ($P=0.236$; Fig. 1A). Median EFS durations were 12.5 months and 6.2 months after Z-BuCyE and BuCyE, respectively. The median duration of CR was 15.9 months after Z-BuCyE and 7.7 months

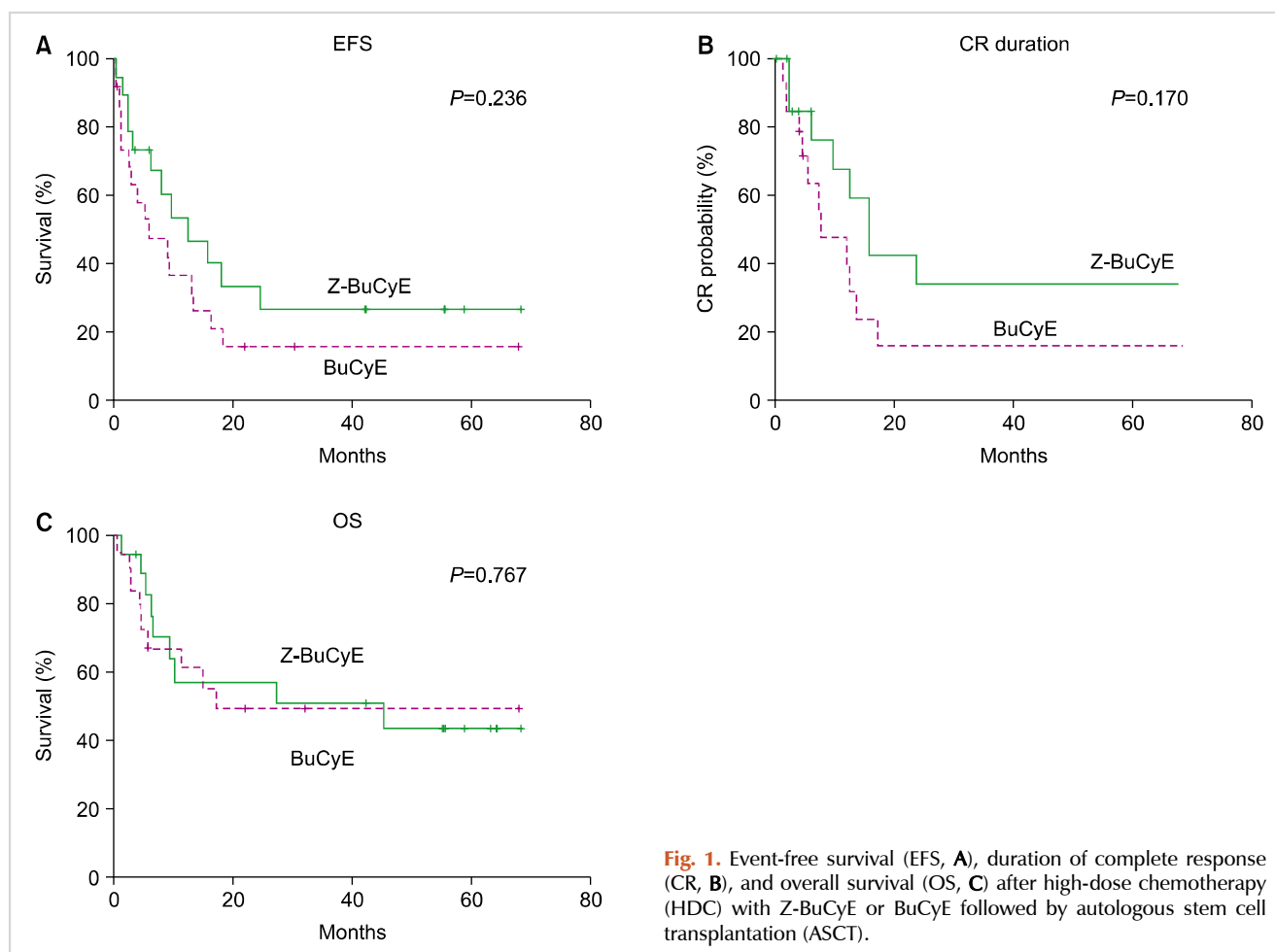


Fig. 1. Event-free survival (EFS, **A**), duration of complete response (CR, **B**), and overall survival (OS, **C**) after high-dose chemotherapy (HDC) with Z-BuCyE or BuCyE followed by autologous stem cell transplantation (ASCT).

Table 4. Relapse and death events.

	BuCyE (N=19)	Z-BuCyE (N=19)
Numbers of relapse/progression events	14 (73.7%)	10 (52.6%)
Numbers of death events	9 (47.4%)	9 (47.4%)
Cause of death		
Relapse/disease progression	7	8
Infection	2	0
Veno-occlusive disease	0	1

after BuCyE ($P=0.170$; Fig. 1B). The 3-year OS rate in the Z-BuCyE and the BuCyE groups were 51% and 49%, respectively ($P=0.767$; Fig. 1C). No statistical difference in EFS and OS was observed with regard to age (>55 years vs. ≤ 55 years), histology (DLBCL vs. others), disease status at ASCT (CR vs. non-CR), and the number of prior chemotherapy regimens (2 vs. 3).

Relapse and death events are listed in Table 4. In the BuCyE group, 11 of 14 relapsed patients underwent further chemotherapy, whereas in the Z-BuCyE group, 9 of 10 underwent palliative chemotherapy or radiotherapy.

DISCUSSION

RIT combines the effects of radiotherapy with immunologic targeting of cell-type-specific monoclonal antibodies for treating lymphoma. Our findings suggest that incorporating ibritumomab tiuxetan into treatment with BuCyE compared with BuCyE alone for ASCT is feasible and may provide additional benefits for patients with relapsed or refractory B-cell NHL.

Our EFS findings are consistent with results of previous studies, suggesting a potential benefit of ibritumomab tiuxetan administration for patients receiving BuCyE followed by ASCT. For example, several studies comparing Z-BEAM with BEAM alone have reported improved efficacy for patients with B-cell NHL. Krishnan *et al.* demonstrated favorable outcomes in 65 patients with aggressive NHL, with 2-year EFS rates of 72% and 67% in the Z-BuCyE and BuCyE groups, respectively [12]. A randomized phase II study reported a trend toward improved EFS at 2 years in the Z-BEAM group (N=22) of 59% versus 37% for the BEAM group (N=21) [13]. In this study, improved EFS in the Z-BuCyE group is likely attributable to the prolonged CR duration after Z-BuCyE conditioning compared with that after BuCyE conditioning (15.9 months versus 7.7 months). As an additive effect of RIT in ASCT, RIT agents such as ibritumomab tiuxetan appear to have advantages based on the emission of β -particles, which can penetrate several millimeters [21, 22]. Hence, RIT with ibritumomab tiuxetan makes it possible to deliver a therapeutic dose of radiation not only to nearby lymphoma cells, but also to neighboring cells that are farther from the tumor surface. This feature may prolong the duration of the response [23, 24].

RIT alone is associated with hematologic toxicities. However, hematologic toxicities observed following RIT can be overcome using SC infusion [25, 26]. In the current study, toxicity profiles of the patients in the Z-BuCyE group were comparable with those of the BuCyE group patients, although 1 patient in the Z-BuCyE group died from VOD. Ibritumomab tiuxetan appears to be safely incorporated into myeloablative regimens, as life-threatening hematologic toxicities associated with RIT and HDC were rescued with ASCT, which was demonstrated by only 1 patient who experienced septicemia. This favorable toxicity profile is encouraging, considering that most patients enrolled in this cohort were middle-aged or elderly.

Till the time of manuscript preparation, no patients in this cohort had developed secondary malignancy. Although there are concerns regarding the development of secondary malignancies following RIT combined with ASCT, secondary malignancies with high-dose Z-BEAM have been observed in only 7% of patients, which is similar to the rate observed with HDC alone [27, 28]. Moreover, adverse events were similar to those seen with BEAM alone [8-12]. Data from a larger number of patients with a longer duration of follow-up are required to properly evaluate the probability of developing secondary malignancies.

Survival outcomes for the cohort appear to be numerically inferior compared with our previous results [16, 17]. Although the CR rates of 78.9% and 73.7% in the Z-BuCyE and BuCyE groups after ASCT were relatively high, EFS and OS data in this study were not promising. This may be due, at least in part, to adverse patient characteristics such as multiple extranodal involvement, as well as extensive previous treatment (chemotherapy and/or radiotherapy) (Table 1) [29, 30].

Nevertheless, because of the similarities between the Z-BuCyE and BuCyE groups in terms of disease-related characteristics affecting prognosis such as histology, disease status at the time of salvage, and the number of prior regimens, our results may provide further information about the role of ibritumomab tiuxetan in conditioning regimens in combination with ASCT.

This study has some limitations. The study was retrospective in nature, included a small number of patients with a relatively short follow-up period, and involved a selected group of patients with relatively poor clinical features. Nevertheless, the patient cohort was derived from patients treated with a uniform treatment protocol in a single center.

In conclusion, our findings suggest that the use of ibritumomab tiuxetan in combination with BuCyE may increase treatment efficacy as well as reduce treatment toxicity and yield an engraftment profile similar to that of BuCyE alone. These observations should be further examined in a randomized study to define the role of RIT for treating lymphoma patients.

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