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ORIGINAL ARTICLE

A phase I/II study of bortezomib plus CHOP every 2 weeks (CHOP-14) in patients with advanced-stage diffuse large B-cell lymphomas

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Background

Bortezomib targets molecular dysregulation of nuclear factor-κB activation and cell cycle control, which are characteristic features of diffuse large B-cell lymphoma (DLBCL). We evaluated the safety and efficacy of bortezomib treatment with dose-dense cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) every 2 weeks (CHOP-14).

Methods

Untreated DLBCL patients were enrolled. A phase I dose-escalation study with 1.0, 1.3, and 1.6 mg/m^2 bortezomib administration on day 1 and 4 in addition to the CHOP-14 regimen was performed to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT). Lenograstim 5 μg/kg/d was administered on day 4-13. The bortezomib dose from the phase I study was used in the phase II study.

Results

Nine and 37 patients were enrolled in the phase I and phase II studies, respectively. The analysis of the phase II results (40 patients) included data of the 3 patients in the last MTD dose cohort of the phase I trial. During the phase I trial, no DLT was observed at any bortezomib dose; therefore, the recommended dose was 1.6 mg/m^2. In phase II, the overall response rate was 95% (complete response: 80%; partial response: 15%). Nine out of the 40 patients showed grade 3 sensory neuropathy, and 22 required at least 1 dose reduction. Three patients could not complete the intended 6 cycles of treatment because of severe neuropathy.

Conclusion

Bortezomib plus CHOP-14 was highly effective for the treatment of untreated DLBCL patients, but in many cases, dose or schedule modification was required to reduce neurotoxicity.

Key Words Bortezomib, CHOP-14, Diffuse large B-cell lymphoma

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive B-cell disorder and the most common lymphoma subtype in adults [1]. Patients without risk factors generally have a favorable prognosis, whereas patients with a resistant or recurrent form of the disease often have unfavorable outcomes. Although the addition of rituximab (R) to the chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has improved outcomes for patients with advanced-stage DLBCL [2-4], treatment resistance is a common problem; thus, more effective strategies are necessary to further improve patient outcomes [1]. Moreover, dose intensification of CHOP by shortening the interval between cycles to 14 days (CHOP-14) also improved

survival rates, but these rates remain unsatisfactory [5-9]. Therefore, new active drugs and treatment strategies are needed to improve outcomes in patients with advanced DLBCL.

Bortezomib, a novel small-molecule proteasome inhibitor, has demonstrated single-agent activity in patients with mantle cell lymphoma [10, 11]. Bortezomib inhibits nuclear factor-κB (NF-κB) activation and has been shown to induce apoptosis and sensitize tumor cells to chemotherapy and radiation [12]. Gene expression profiling studies of DLBCL have identified overexpression of NF-κB as a potential therapeutic target in the activated B-cell (ABC) subtype of DLBCL; patients with this subtype have shown poorer outcomes in response to conventional chemotherapy than those with the germinal center B cell (GCB) subtype of DLBCL [13, 14]. Although bortezomib has minimal efficacy as a single agent in patients with refractory and recurrent DLBCL, its combination with dose-adjusted chemotherapy is not associated with significant increase in toxicity, suggesting that bortezomib may be safely combined with chemotherapy [1, 13].

We conducted a phase I/II trial of bortezomib in combination with CHOP-14 in previously untreated patients with advanced-stage DLBCL. Because of the potential for overlapping toxicities, we initiated the study by performing a phase I dose-escalation of bortezomib plus CHOP-14 to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of bortezomib. Using the bortezomib dose from the phase I trial, we performed a phase II trial to test the efficacy and safety of bortezomib plus CHOP-14 in patients with advanced-stage DLBCL. This study was registered at www.clinicaltrials.gov as NCT00379574.

MATERIALS AND METHODS

1. Patients

Patients aged <70 years with histologically confirmed DLBCL and no prior history of any anti-cancer treatment, including chemotherapy or radiotherapy, were eligible. All patients had the following characteristics: an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; at least 1 unidimensionally measurable lesion; and adequate organ functions, defined as absolute neutrophil count (ANC) of ≥1,500/mm^3, platelet count of ≥75,000/mm^3, serum creatinine level of ≤2.0 mg/dL, estimated creatinine clearance of ≥50 mL/min, bilirubin level of <1.25× the upper limit of normal (ULN), and serum aminotransferase level ≤2.5 ×ULN. Patients with any of the following characteristics were excluded: grade 2 or higher peripheral neuropathy; a history of hypersensitivity to bortezomib, boron, or mannitol; or a serious medical or psychiatric illness. Women who were pregnant or breast-feeding were also excluded from the study. The study was approved by the ethics committee of each participating institution, and all patients were provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2. Study design and treatment

This study had a non-comparative phase I/II design. In phase I, we identified the MTD of bortezomib when it was combined with the CHOP-14 regimen, which was the recommended dose for phase II. In phase II, we evaluated the efficacy and safety of the bortezomib plus CHOP-14 regimen.

CHOP-14 treatment consisted of cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 (up to 2 mg/m^2) on day 1, and prednisolone 100 mg/d on day 1 through 5 every 14 days. The maximum number of cycles was 6, unless patients showed progressive disease or unacceptable toxicity, or withdrew consent. Patients also received 5 μg/kg/d lenograstim (Neutrogin®, JW Pharmaceutical Corp., Seoul, Korea) subcutaneously on day 4-13. Bortezomib was administered on day 1 and 4.

In phase I, bortezomib was administered at doses of 1.0, 1.3, and 1.6 mg/m^2 to consecutive cohorts with 3 patients each; dose escalation over 1.6 mg/m^2 was not planned according to a previous phase I study of bortezomib and CHOP-21 [15, 16]. DLTs were defined as grade 4 neutropenia associated with fever for more than 3 days; grade 4 neutropenia lasting for more than 10 days; grade 3-4 thrombocytopenia with grade 2 hemorrhage; or grade 3-4 non-hematologic toxicity during the first treatment cycle.

Three patients were enrolled at each dose level, and dose escalation continued, if no DLT was observed in any of the patients; however, intra-patient dose escalation was not allowed. When DLT was observed in a single patient, 3 additional patients were treated with the same dose. When 2 or more of 6 patients developed DLT, the previous dose level was considered as the MTD. When only 1 of 6 patients developed DLT, dose escalation continued.

Patients with an ANC of ≥1,500/mm^3, platelet count of ≥75,000/mm^3, and non-hematologic toxicity of ≤grade 1 were administered the same treatment as that in the previous treatment cycle. Doses of cyclophosphamide and doxorubicin were reduced by 25%, if ANC and platelet recovery exceeded 1 week; the doses were reduced by 50%, if the delay was more than 2 weeks. When a 3-week delay was required to recover from bortezomib-related toxicity, bortezomib dose was reduced by 1 dose level (e.g., from 1.6 to 1.3 mg/m^2) in the subsequent cycles. If the next cycle was also delayed for more than 3 weeks because of toxicity, the subject was withdrawn from the study.

During phase II, we evaluated the complete response (CR) rate, event-free survival (EFS), overall survival (OS), and safety of the bortezomib plus CHOP-14 regimen.

3. Evaluation

Toxicity was evaluated every week by history taking, physical examination, complete blood counts, biochemical tests, and other appropriate studies. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3. Treatment response was evaluated after 3 cycles and 6 cycles by using the International Working

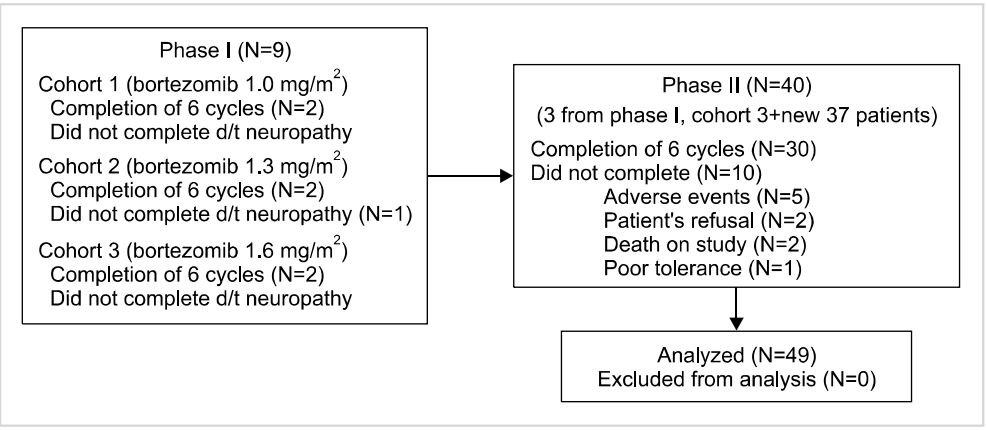

Fig. 1. Profile of the phase I and phase II trials.

Group response criteria [17]. After the end-of-study visit, patients were followed every 4-12 weeks for a minimum of 2 years after enrollment and if possible for 5 years.

All time-to-event variables were estimated using the Kaplan-Meier method. EFS was defined as the interval between the date of start of treatment and the date of documented disease progression or death from any cause, whichever happened first. OS was defined as the interval between the date of start of treatment and date of death from any cause.

RESULTS

1. Patients

Nine patients were enrolled between December 2006 and April 2007 for the phase I study, and 37 patients were subsequently enrolled until November 2009 for the phase II study. The phase II study included 40 patients, including 3 patients from cohort 3 of the phase I study (Fig. 1). Patient characteristics are summarized in Table 1. The median patient age was 54 years (range, 27-70 years), and most patients (71.4%) had stage IV disease.

2. Phase I determination of bortezomib dose

No DLT was seen at the 3 dose levels of bortezomib (1.0, 1.3, and 1.6 mg/m^2) during the first cycle. Therefore, the recommended dose of bortezomib for phase II was determined to be 1.6 mg/m^2 when combined with CHOP-14. A patient in cohort 1 (dose, 1.0 mg/m^2 bortezomib) refused to receive bortezomib on d 4 of cycle 6 because of grade 2 neuropathic pain; this patient was not replaced. In cohort 2 (dose, 1.3 mg/m^2), a patient showed disease progression after 5 cycles and received salvage chemotherapy. In cohort 3 (dose, 1.6 mg/m^2), 1 patient experienced grade 3 abdominal pain with nausea and vomiting, followed by paralytic ileus after the second cycle. Because these symptoms were determined to be associated with treatment-related neuropathy, which did not resolve to grade 1 within 3 weeks, the patient was dropped from the study. This patient, however, was treated with CHOP-14, without bortezomib, during cycles 3-6. There were no other dose reductions or delays.

Table 1. Baseline characteristics of the patients (N=49).

Age	
Median (Range), yr	54 (27-70)
Gender	
Male	25 (51.5%)
Female	24 (48.5%)
Ann Arbor stage	
II	4 (8.2%)
III	10 (20.4%)
IV	26 (71.4%)
B symptom	
Yes	22 (44.9%)
No	27 (55.1%)
ECOG performance status	
0	10 (20.4%)
1	18 (36.7%)
2	21 (42.9%)
Extranodal involvement	
0-1	31 (63.3%)
>1	18 (36.7%)
Bone marrow involvement	
Yes	4 (8.2%)
No	45 (91.8%)
Age-adjusted IPI	
Low risk	6 (12.2%)
Low intermediate risk	23 (46.9%)
High intermediate risk	13 (26.5%)
High risk	7 (14.4%)

Abbreviations: IPI, international prognostic index; ECOG, Eastern Cooperative Oncology Group.

3. Disposition of patients and treatment delivery

The most common reason for withdrawal from either phase was adverse events. In the phase I study, 1 of the 3 patients in cohort 1 failed to complete the 6 cycles of treatment because of neuropathic pain, and 1 patient of 3 in cohort 3 failed to complete treatment because of paralytic ileus accompanied by neuropathy (Fig. 1). One patient in cohort 2 showed progressive disease before completion of the 6 cycles of therapy and stopped treatment.

In phase II, 30 patients (75.0%) completed 6 cycles of bortezomib plus CHOP-14; 10 patients did not complete treatment. Five patients discontinued treatment because of severe adverse events, including severe sensory neuropathy,

Table 2. Adverse events after bortezomib plus CHOP-14 treatment (N=49).

Grade	Phase I (N=9)							Phase II (N=40)	
	Bortezomib dose (mg/m^2)								
	1.0 (N=3)		1.3 (N=3)		1.6 (N=3)		All doses	1.6	
	3	4	3	4	3	4		3	4
Hematologic, N (%)									
Anemia	-	-	-	-	1	-	1 (11.1%)	17 (42.5%)	4 (10.0%)
Thrombocytopenia	-	-	1	-	-	1	2 (22.2%)	5 (12.5%)	6 (15.0%)
Neutropenia	-	-	-	1	-	1	2 (22.2%)	3 (7.5%)	9 (22.5%)
Febrile neutropenia	-	-	1	-	-	-	1 (11.1%)	6 (15.0%)	-
Non-hematologic, N (%)									
Abdominal pain	-	-	-	-	1	-	1 (11.1%)	3 (7.5%)	-
Anorexia	-	-	-	-	-	-	-	-	-
Constipation	-	-	-	-	-	-	-	-	1 (2.5%)
Diarrhea	-	-	-	-	-	-	-	4 (10.0%)	1 (2.5%)
Fever	-	-	-	-	-	-	-	4 (10.0%)	-
Fatigue	-	-	-	-	-	-	-	2 (5.0%)	-
Nausea	-	-	-	-	1	-	1 (11.1%)	-	-
Vomiting	-	-	-	-	1	-	1 (11.1%)	1 (2.5%)	-
Hyperglycemia	-	-	-	-	-	-	-	4 (10.0%)	-
Hypoalbuminemia	-	-	-	-	-	-	-	5 (12.5%)	-
Hypocalcemia	-	-	-	-	-	-	-	4 (10.0%)	1 (2.5%)
Hypokalemia	-	-	-	-	-	-	-	3 (7.5%)	-
Sensory neuropathy	-	-	1	-	1	-	2 (22.2%)	9 (22.5%)	-
Motor neuropathy	-	-	-	-	-	-	-	3 (7.5%)	-

severe infection, small bowel perforation, pneumonitis with bilateral pulmonary infiltration, and uncontrolled delirium; each of these events was observed in 1 patient. Two patients refused to continue treatment; 2 died of severe pneumonia with septic shock during treatment; and 1 showed poor tolerance to treatment followed by rapid disease progression. Overall, 40 patients received 214 cycles of bortezomib plus CHOP-14. The median number of cycles administered per patient was 6. The mean percentages of the planned doses (i.e., the actual dose divided by the planned full dose) of bortezomib, cyclophosphamide, vincristine, and doxorubicin were 90.6%, 99.2%, 98.6%, and 99.2%, respectively.

4. Toxicity

Grade 3 or 4 adverse events during phases I and II are summarized in Table 2. During both phases, myelosuppression was rare. Among non-hematologic toxicities, sensory neuropathy was the most common adverse event, occurring in 22.2% of patients in both phases I and II; 9 patients showed grade 3 sensory neuropathy (3 patients after 3 cycles of treatment and 6 patients after 4 cycles of treatment). Three patients showed grade 3 motor neuropathy. Grade 1 and 2 neuropathy was also common, occurring in 17.5% (grade 1) and 30.0% (grade 2) of patients, respectively.

Of the 40 patients in the phase II trial, 22 (55.0%) required bortezomib dose reduction from 1.6 mg/m^2 to 1.3 mg/m^2 because of toxicities. The most common toxicity was grade ≥3 neuropathy, which occurred after median 4 cycles of treatment. Three patients required 2 dose reductions of bortezomib from 1.6 mg/m^2 to 1.0 mg/m^2 because of neuropathy.

Table 3. Response after bortezomib plus CHOP-14 treatment.

	Phase I		Phase II
	Bortezomib dose (mg/m^2)		
	1.0 (N=3)	1.3 (N=3)	1.6 (N=40)
After 3 cycles			
CR	2	2	25 (62.5%)
PR	1	1	13 (32.5%)
SD	0	0	0 (0.0%)
PD	0	0	0 (0.0%)
Not available	0	0	2 (5.0%)
After completion of treatment			
CR	3	2	32 (80.0%)
PR	0	0	6 (15.0%)
SD	0	0	0 (0.0%)
PD	0	1	0 (0.0%)
Not available	0	0	2 (5.0%)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

5. Response

Two patients in cohort 1 of phase I achieved CR, 1 patient achieved PR after 3 cycles of treatment. In cohort 2 of phase I, all 3 achieved CR after completion of treatment and 2 patients achieved CR and 1 achieved PR after 3 cycles of treatment; however, 1 patient showed tumor progression after completion of treatment (Table 3).

In phase II, 25 patients achieved CR and 13 patients achieved PR after 3 cycles of treatment. After completion of

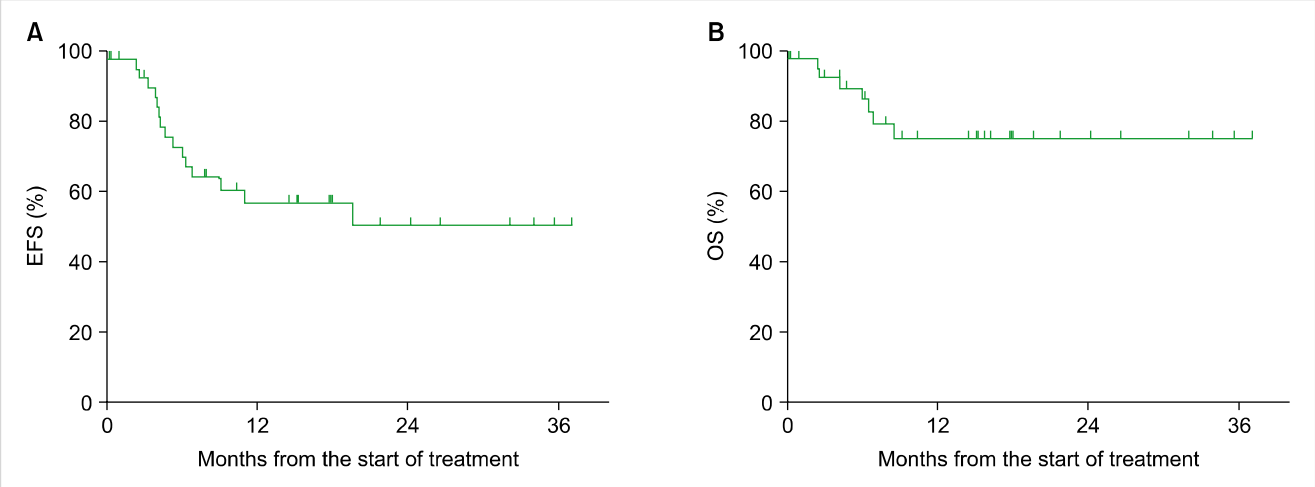

Fig. 2. **(A)** Event-free survival (EFS) and **(B)** overall survival (OS) of patients in the phase II study.

treatment, 32 patients achieved CR and 6 patients achieved PR, with an overall response rate (ORR) of 95%. At median follow-up of 16.1 months, 10 patients showed disease progression or relapse and 8 died. The overall 2-year EFS rate was 60.6% and the 2-year OS rate was 75.1% (Fig. 2).

DISCUSSION

We evaluated the safety and efficacy of the bortezomib plus dose-dense CHOP-14 regimen in patients with advanced-stage DLBCL. Although no DLT was observed during the first cycle of the phase I study and the MTD was not reached, we utilized a bortezomib dose of 1.6 mg/m^2 in the phase II trial; this dosage showed low toxicity in prior phase I/II trials [15, 16, 18].

Our phase II trial showed that treatment with 1.6 mg/m^2 bortezomib in addition to the CHOP-14 regimen on day 1 and 4 resulted in an overall response rate of 95%, including CR rate of 80% and PR rate of 15%. However, 9 of the 40 patients (22.5%) experienced grade 3 sensory neuropathy; 22 patients (55.0%) required at least 1 bortezomib dose reduction after 4 cycles of treatment, despite close monitoring and assessment of neuropathy using functional assessment of cancer therapy-neurotoxicity (FACT-NTX). In addition, 3 patients could not complete the 6 scheduled cycles of bortezomib plus CHOP-14 due to severe neuropathy.

Neurotoxicity is a dose-limiting adverse effect of bortezomib, but the mechanism by which bortezomib induces peripheral neuropathy is still unclear. It is believed to be due, at least in part, to damage of mitochondria and the endoplasmic reticulum caused by the activation of the mitochondrial-based apoptotic pathway [19]. In patients with multiple myeloma, the incidence of neuropathy increases with the cumulative dose of bortezomib, often reaching a plateau after the first 5 cycles in patients treated with single-agent bortezomib. Because prolonged proteasome inhibition is likely to result in increased neurotoxicity, determination of the DLT after only 1 cycle of treatment in our phase I trial may not be suitable for evaluating the neurotoxicity observed after 6 cycles.

Several studies using the combination of bortezomib plus chemotherapy have been undertaken or are ongoing. The overlapping neurotoxicities of vincristine and bortezomib have limited the success of these trials. In combination with DA-EPOCH, the MTD of bortezomib was 1.7 mg/m^2 (day 1 and 4) in patients with previously treated DLBC [20]. However, the subsequent phase 2 trial used a bortezomib dose of 1.5 mg/m^2 because neuropathy resulted in discontinuation of bortezomib after the patient had received multiple doses of the drug. However, in patients with untreated indolent B-cell lymphoma, bortezomib doses of up to 1.6 mg/m^2 were added to the R-CHOP regimen on day 1 and 8, with vincristine capped at a dose of 1.5 mg. At these doses, treatment was well tolerated, with only 1 patient experiencing grade 3 neuropathy [21]. A recent randomized phase 2 study comparing 2 schedules of bortezomib plus R-CHOP also showed that neurological toxicity was more frequent and severe when bortezomib was administered biweekly (days 1, 4, 8, and 11) rather than weekly (days 1 and 8) [22]. Another phase 2 study, which used 1.3 mg/m^2 bortezomib with standard doses of R-CVP (BR-CVP; bortezomib, rituximab, cyclophosphpamide, vincristine, and prednisolone) in patients with advanced-stage follicular lymphoma, found that no patient developed grade 4 neurotoxicity and only 5% developed grade 3 neurotoxicity [23]. Therefore, neurotoxicity in patients treated with bortezomib plus CHOP-14 may be reduced by modifying the bortezomib dose or schedule (days 1 and 8 rather than days 1 and 4), or by reducing or eliminating the dose of vincristine in the CHOP-14 regimen.

The overall response rate after treatment with bortezomib plus CHOP-14 was 95%, with 80% of patients achieving CR. These response rates were higher than those observed with R-CHOP-14 (ORR: 77%, including 43% CR, 20% CR, and 14% PR) and even R-CHOEP (cyclophosphamide, doxor-

ubicin, vincristine, etoposide, and prednisolone) -14 (ORR: 91%, including 53% CR, 25% CRu, and 13% PR). Because 62.5% of our patients achieved CR after just 3 cycles of treatment, the combination of bortezomib with CHOP-14 may induce an early treatment response.

The activity of the NF-κB signaling pathway is a distinguishing feature of the ABC subtype of DLBCL, which has a poorer prognosis than the GCB subtype when treated with doxorubicin-containing chemotherapy [21, 22, 24]. Bortezomib enhanced the activity of chemotherapy in cases involving the ABC, but not the GCB subtype of DLBCL, providing a rational therapeutic approach based on genetically distinct DLBCL subtypes [1]. We could not analyze differences in efficacy on the basis of the DLBCL subtypes due to a lack of information on gene expression profiling and immunohistochemical analysis of tumors. Furthermore, although we found that bortezomib plus CHOP yielded a high response rate in DLBCL patients, we did not compare this regimen with R-CHOP, which is the current standard of care for DLBCL; therefore, further investigations of the efficacy of our regimen are necessary prior to its acceptance as another treatment option.

The major limitation of this study was that none of our DLBCL patients was treated with rituximab. Trials of bortezomib plus R-CHOP were in progress when we planned this trial. The Korean Food and Drug Administration recently approved the use of rituximab with CHOP every 3 weeks in patients with DLBCL. This study was initiated before the publication of the MInT [4] and RICOVER-60 trials [25]. These administrative issues and limited research funds were responsible for the absence of rituximab in our treatment protocol.

In conclusion, we found that the combination of bortezomib with CHOP-14 showed a high response rate in untreated DLBCL patients. However, modification of the dose or schedule of bortezomib is needed to reduce neurotoxicity.

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