Phase I study of proteasome inhibitor bortezomib plus CHOP in patients with advanced, aggressive T-cell or NK/T-cell lymphoma

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The aim of the study was to determine the maximum tolerated dose (MTD) and safety of the combination of bortezomib and cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) as first-line therapy in advanced, aggressive T-cell lymphoma. Patients received increasing doses of bortezomib on days 1 and 8 (weekly schedule, 1.0, 1.3, and 1.6 mg/m²/dose) in addition to 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, 1.4 mg/m² vincristine on day 1 and 100 mg/day prednisolone on days 1 to 5, every 3 weeks. Six cycles of therapy administered every 21 days were planned. Thirteen patients, who had stage III/IV chemotherapy-naive aggressive T-cell lymphoma, received a total of 55 cycles of treatment. One patient experienced hematologic dose-limiting toxicity (grade 4 neutropenia associated with febrile episode) at the 1.0 mg/m²/dose of bortezomib. There was no dose-limiting non-hematologic toxicity. The MTD was not reached at 1.6 mg/m² dose level of bortezomib. The overall complete remission rate in all patients was 61.5% (95% confidence interval = 31.6–86.1). Bortezomib can be safely combined with CHOP chemotherapy and constitutes an active regimen in advanced-stage, aggressive T-cell lymphoma patients. The recommended dose for subsequent phase II studies of bortezomib plus CHOP is 1.6 mg/m²/dose of bortezomib on days 1 and 8 every 3 weeks as first-line treatment.

Key words: bortezomib, chemotherapy, non-Hodgkin’s lymphoma

Introduction

Peripheral T-cell lymphomas (PTCLs) constitute biologically heterogeneous groups of lymphomas and demonstrate poor prognosis when treated with the conventional chemotherapy regimens used in aggressive B-cell lymphomas. Recent studies including ours have shown little benefit from doxorubicin-based or cisplatin-based chemotherapy in PTCL [1,2,3]. Importantly, the T-cell immunophenotype was shown as an independent adverse prognostic factor in several studies [4,5,6]. In Korea, PTCLs including T- or natural killer (NK)-cell lymphomas constitute ~25%–35% of all non-Hodgkin’s lymphomas [7, 8]. On the basis of previous studies, 5-year overall survival rates ranged between 30% and 40% for patients with PTCL or extranasal NK/T-cell lymphoma (ENKL) following conventional doxorubicin-based chemotherapy [9,10,11,12]. Furthermore, our retrospective study showed 0% complete remission (CR) rate in NK/T-cell lymphoma patients with advanced stage following anthracycline-based chemotherapy [mostly cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen] [13]. Undoubtedly, there is an urgent need for novel treatment modalities in advanced-stage, aggressive T-cell lymphomas.

Bortezomib, a dipeptide boronic acid that selectively and potently inhibits the proteasome 26S complex, has demonstrated activity in hematologic malignancies, most commonly multiple myeloma [14,15,16]. Among the proteins degraded by the ubiquitin–proteasome pathway is the inhibitory protein IκB, which inhibits nuclear factor kappa B (NF-κB). In response to an external stressor such as radiotherapy or chemotherapy, IκB is phosphorylated, ubiquitinated, and degraded by proteasome [17]. NF-κB then translocates to the nucleus, where it activates antiapoptotic and cell growth genes. The inhibition of the proteasome via bortezomib prevents degradation of IκB and down-regulates NF-κB-mediated transcriptional activation, potentially...
sensitizing resistant cells to the effects of chemotherapeutic agents or radiotherapy [17].

A constitutively active NF-κB signaling has been previously revealed by the Hong Kong group in ENKL [18]. Moreover, preclinical studies have shown that bortezomib dramatically inhibited tumor growth with tolerable toxicity in ENKL as a single agent [19]. Co-treatment of mantle cell lymphoma cell lines with bortezomib plus doxorubicin, vincristine, and 4-hydroperoxycyclophosphamide was shown to produce a synergistic effect, which was greater if cells were sequentially treated with doxorubicin or vincristine and then bortezomib [20].

On the basis of these data, we conducted a phase I study of bortezomib in combination with CHOP as first-line therapy in patients with advanced-stage, aggressive T-cell lymphoma. The aim of the study was to determine the maximum tolerated dose (MTD) and safety profile of the combination regimen.

**patients and methods**

**patient eligibility**

Patients who satisfied all the following criteria were enrolled into the study: (i) histologically confirmed PTCLs and NK/T-cell lymphomas excluding ALK-positive anaplastic large-cell T-cell lymphomas (ALCL); (ii) performance status (Eastern Cooperative Oncology Group) of three or less; (iii) age ≥56 years; (iv) at least one or more unidimensionally measurable lesions (≥2 cm by conventional computerized tomography (CT) or ≥1 cm by spiral CT or skin lesions or a measurable lesion by physical examination); (v) adequate renal function (serum creatinine ≤1.3 mg/dl or creatinine clearance ≥60 ml/min); (vi) adequate hepatic function (serum transaminases ≤3× upper normal limit, bilirubin <1.5 mg/dl); (vii) adequate bone marrow function (neutrophil count ≥75 000/l and platelets ≥250 000/l); (viii) prior treatment of the disease; and (ix) Ann Arbor stage III or IV. Patients with any other malignancies within the past 5 years except skin basal cell carcinoma or carcinoma in situ of cervix were excluded from the study. Patients with central nervous system involvement and HIV positivity were also excluded from the study. All patients provided a written informed consent before any study-related procedure was administered. The protocol was approved by the institutional review board before the study initiation. All pathologic specimens were reviewed by one pathologist in accordance with the World Health Organization criteria for pathologic diagnosis [21].

**drug administrations**

Six cycles of therapy administered every 21 days were planned. The CHOP regimen consisted of 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, 1.4 mg/m² vincristine (maximum 2 mg) vincristine on day 1 and 100 mg/day prednisolone on days 1 to 5, every 3 weeks. The initial dose level of bortezomib was 1.0 mg/m²/dose. Two recent phase I trials with bortezomib, the starting dose was set lower than the recommended dose levels: 1.3, and 1.6 mg/m² on days 1 and 8, every 3 weeks. Dose escalation and reduction were on the basis of the continual reassessment method, with at least two patients per dose level and no dose level skipped. No intrapatient dose escalation will be allowed. If one patient experienced dose-limiting toxicity (DLT), three additional patients were added to the dose level. If two of six patients experienced DLT, the previous dose level was declared the MTD. If only one of six patients experienced DLT, dose escalation was permitted to continue. DLT refers only to toxic events that occur during the first cycle of treatment. DLT was defined as follows: grade 4 hematologic toxic effects, grade 3 or greater non-hematologic toxic effects (except for any grade of alopecia, grade 3 nausea, and vomiting or diarrhea in the absence of maximum antidiarrheal therapy), or grade 3 thrombocytopenia with grade 2 hemorrhage. Prophylactic granulocyte colony stimulating factor was not permitted in this protocol.

**dose modifications**

Weekly complete blood count was checked to assess hematologic toxic effects at first cycle. If absolute neutrophil count (ANC) was <1000/µl or platelet <75 000/µl, administration of chemotherapeutic drugs was delayed 1 week. If ANC was >1000/µl and platelet >75 000/µl after a week delay, chemotherapy was administered without dose reductions. If ANC was <1000/µl or platelet <75 000/µl after a week delay, chemotherapy was delayed for one additional week. If ANC was >1000/µl and platelet count >275 000/µl following a 2-week delay from the planned date of chemotherapy, doses of cyclophosphamide and doxorubicin were reduced by 25%. If patients required a delay of ≥2 weeks for recovery, patients went off the study protocol. On day 8 of bortezomib administration during the first cycle, the hematology results must be platelet count ≥30 000/µl and ANC ≥275 000/µl. If the above parameters were not met, the bortezomib dose was skipped; the dose was not given later in the cycle. If day 8 bortezomib was skipped due to hematologic toxicity, the dose of bortezomib was reduced in the subsequent cycles from 1.6 to 1.3 mg/m², 1.3 to 1.0 mg/m², or 1.0 to 0.7 mg/m².

**evaluation**

Evaluations were made after three and six cycles via physical examination, blood testing, and computed tomography scan. For patients with bone marrow involvement, follow-up bone marrow aspiration and biopsy were included for evaluation. Response was defined according to previously reported international criteria [24]. Adverse events were graded according to Common Terminology Criteria for Adverse Events v.3.

**results**

**patient characteristics**

Thirteen patients were enrolled on to the study. All patients were assessable for toxicity and treatment response. Patient characteristics are provided in Table 1. The median age of patients was 53 years (range 18–65 years). The histologic distributions were as follows: seven peripheral T cell lymphoma, unspecified, three ENKLs, two angioimmunoblastic T-cell lymphomas, and one ALK-negative anaplastic large-cell lymphoma. Over 90% had performance status less than one, and two-thirds of the patients had low to low-intermediate International Prognostic Index. All the enrolled patients received bortezomib + CHOP as first-line treatment of lymphoma.

**drug delivery**

The number of patients and cycles administered at different dose levels are listed in Table 2. At the 1.0 mg/m²/dose level of bortezomib, one patient did not receive day 8 bortezomib in cycle 4 due to grade 4 neutropenia and dose was reduced subsequently according to the protocol. At the 1.6 mg/m²/dose level of bortezomib, chemotherapy was delayed for 1 week due to poor performance in one patient; however, full dose was given upon recovery. Otherwise, there were no dose reductions or delays in scheduled chemotherapeutic drug administration due to medical causes.
The second patient treated at the 1.0 mg/m²/dose of bortezomib developed hematologic DLT (grade 4 neutropenia associated with febrile episode) (Table 3). There was no dose-limiting non-hematologic toxicity. There were only two patients at the 1.0 mg/m²/dose level of bortezomib and one patient in each 1.3 and 1.6 mg/m²/dose levels of bortezomib who experienced grade 1 peripheral sensory neuropathy. No dose adjustments were required due to peripheral neuropathy at all three levels.

treatment response
All patients were assessable for response. The overall response rate and the CR rates in all patients were 61.5% [95% confidence interval (CI) = 31.6–86.1]. The CR rates according to histologic subtypes were as follows: PTCLu (five of seven, 71.4%), ALCL (one of one, 100%), angioimmunoblastic lymphoproliferative disease (one of two, 50%), and ENKL (one of three, 33.3%). Of the eight patients who attained complete remission, undetermined, three patients relapsed at 3, 4, and 12 months.

discussion
This phase I study was designed to study the feasibility of bortezomib in combination with CHOP in advanced-stage, aggressive T-cell lymphoma. One DLT of grade 4 neutropenia with fever occurred at the 1.0 mg/m²/dose level of bortezomib in the first three-patient cohort; thus, the level I cohort was expanded from three to six patients. There were no hematologic or non-hematologic DLTs observed in subsequent dose levels in this trial. Therefore, the MTD has not been reached and the recommended dose for phase II trial of bortezomib/CHOP is 1.6 mg/m²/dose of bortezomib.

In concurrence with other studies, the addition of bortezomib did not seem to increase toxicity when combined with CHOP. A phase I/II trial of rituximab–CHOP plus bortezomib (standard rituximab–CHOP + bortezomib at 0.7, 1.0, or 1.3 mg/m² on days 1 and 4 of each cycle) as initial therapy for diffuse large B-cell lymphoma (DLBCL) demonstrated 10% grade 2 or greater peripheral neuropathy, 15% grade 4 thrombocytopenia, and 15% grade 4 neutropenia. One of the concerning side-effects for combination of CHOP and bortezomib was peripheral sensory neuropathy. Nevertheless, during a total of 55 cycles, there were only two patients at the 1.0 mg/m²/dose level of bortezomib and one patient in each 1.3 and 1.6 mg/m²/dose levels of bortezomib who experienced grade 1 peripheral sensory neuropathy. No dose adjustments were required due to peripheral neuropathy at all three levels. The frequency of grade 3 or greater hematologic toxic effects did not increase with the dose escalation of bortezomib in this trial. Hematologic toxic effects were mostly neutropenia and there was only one patient who experienced grade 3 thrombocytopenia without bleeding episode.

We evaluated a weekly bortezomib schedule rather than the standard twice-weekly schedule mainly due to its convenience for patients. Several studies explored the weekly bortezomib schedule in various tumor types, although results from a randomized trial comparing the twice-weekly and weekly bortezomib are not available. A phase II study of weekly bortezomib in multiple myeloma patients showed similar response rates and toxicity profile to the standard bortezomib schedule [25]. Other study further demonstrated that a weekly bortezomib (1.0 mg/m², days 1 and 8) combined with a standard gemcitabine/cisplatin regimen was comparable to

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Total no. of patients</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>53 (18–65)</td>
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<tr>
<td>Sex (male)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>PTCLu</td>
<td>7 (54)</td>
</tr>
<tr>
<td>ENKL</td>
<td>3 (23)</td>
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<tr>
<td>AILD</td>
<td>2 (15)</td>
</tr>
<tr>
<td>ALK-negative ALCL</td>
<td>1 (8)</td>
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<tr>
<td>Ann Arbor stage</td>
<td></td>
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<tr>
<td>Stage III</td>
<td>7 (54)</td>
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<td>Stage IV</td>
<td>6 (46)</td>
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<tr>
<td>Performance status</td>
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<tr>
<td>0–1</td>
<td>12 (92)</td>
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<tr>
<td>2</td>
<td>1 (8)</td>
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<tr>
<td>Elevated LDH</td>
<td>7 (54)</td>
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<tr>
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</tr>
<tr>
<td>Low–low-intermediate</td>
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</tr>
<tr>
<td>High–intermediate-high</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Bulky disease (≥10 cm)</td>
<td>5 (38)</td>
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<tr>
<td>Bone marrow involvement</td>
<td>1 (8)</td>
</tr>
<tr>
<td>B symptom (+)</td>
<td>4 (31)</td>
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</tbody>
</table>

PTCLu, peripheral T-cell lymphoma, unspecified; ENKL, extranasal NK/T-cell lymphoma; AILD, angioimmunoblastic lymphoproliferative disease; ALCL, anaplastic large-cell T-cell lymphomas; LDH, lactate dehydrogenase.

<table>
<thead>
<tr>
<th>Bortezomib (mg/m²/dose)</th>
<th>Cyclophosphamide (mg/m²/dose)</th>
<th>Doxorubicin (mg/m²/dose)</th>
<th>Total no. of patients</th>
<th>DLT</th>
<th>No. of cycles</th>
<th>Best response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>750</td>
<td>50</td>
<td>7</td>
<td>Grade 4 neutropenia with fever</td>
<td>34</td>
<td>5 CRs, 1 SD, 1 PD</td>
</tr>
<tr>
<td>1.3</td>
<td>750</td>
<td>50</td>
<td>3</td>
<td>None</td>
<td>13</td>
<td>2 SDs, 1 CR</td>
</tr>
<tr>
<td>1.6</td>
<td>750</td>
<td>50</td>
<td>3</td>
<td>None</td>
<td>8</td>
<td>1 CR, 1 CRu, 1 PD</td>
</tr>
</tbody>
</table>

CR, complete remission; SD, stable disease; PD, progressive disease; CRu, complete remission, undetermined.
biweekly bortezomib in terms of efficacy and toxicity, but yet better tolerability by non-small-cell lung cancer patients [26]. A promising antitumor activity of CHOP/bortezomib combination against advanced-stage, aggressive T-cell lymphoma was observed in this study. The overall CR rate was 61.5% (95% CI = 31.6–86.1), which is certainly encouraging considering the fact that all patients had advanced stage at study entry. The remission was durable for 3–12 months. Particularly, patients with PTCLu and ALCL showed better response (71%–100%) than those with AILD or ENKL (33%–50%), although interpretation should be cautioned for small number of patients and inherent nature of phase I study. A possible role of bortezomib as a potential therapeutic agent in T-cell lymphoma has recently been documented in vitro T-cell lymphoma cell line that the positive regulatory domain I, which is related to resistance to chemotherapeutic agents, is down-regulated upon bortezomib treatment [27].

This trial represents the first to investigate the role of bortezomib plus CHOP in patients with advanced T-cell lymphoma. There are several preliminary phase I/II studies on combination of bortezomib and standard chemotherapy in B-cell lymphomas. The combination initial treatment of rituximab–CHOP + bortezomib as initial therapy for DLBCL demonstrated encouraging antitumor activity with CR rate of 68% [28]. Another phase I trial of bortezomib plus twice-weekly CHOP in nine DLBCL patients reported mild toxicity profile with only one patient with progressive disease [29]. Other phase 2 clinical trials reported response rates of 18%–60% in follicular lymphoma and 39%–56% in mantle cell lymphoma [30, 31]. The only published phase II study of a single-agent bortezomib (1.3 mg/m² on days 1, 4, 8, and 11, every 21 days) on T-cell lymphoma recently showed a CR rate of 17% with favorable toxicity profile in 15 patients with advanced-stage, refractory cutaneous T-cell lymphoma [32]. Thus, a CR rate of 61.5% in advanced-stage, aggressive T-cell lymphoma is very promising, and thus a phase II on this novel combination to further test the efficacy is definitely warranted.

In conclusion, bortezomib can be safely combined with CHOP chemotherapy and constitutes an active regimen in advanced-stage, aggressive T-cell lymphoma patients. The recommended dose for subsequent phase II studies of bortezomib plus CHOP is 1.6 mg/m²/dose of bortezomib on days 1 and 8 every 3 weeks as first-line treatment. We are currently conducting phase II trial in this clinical setting to investigate the efficacy and toxicity profile of the regimen.

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references