A phase II study of bortezomib in patients with relapsed or refractory aggressive adult T-cell leukemia/lymphoma

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Bortezomib is a first-in-class reversible inhibitor of the 26S proteasome that has been approved for the treatment of multiple myeloma in many countries and for previously treated mantle cell lymphoma in the US. One of the actions induced by the inhibition of proteasome is blockade of the degradation of IkBα, which prevents the activation of nuclear factor-κB (NF-κB), and this is followed by the modulation of downstream signaling pathways.1(1)

Adult T-cell leukemia/lymphoma (ATL) is a malignancy of peripheral T-lymphocytes with a poor prognosis caused by human T-lymphotropic virus type I.2(2) Adult T-cell leukemia/lymphoma has been divided into four clinical subtypes; acute-, lymphoma-, chronic-, and smoldering-types.3(3) Chronic-type ATL has been further divided into favorable and unfavorable. The standard of care for treatment-naïve aggressive ATL (acute-, lymphoma- and unfavorable chronic-type) has been aggressive chemotherapy using multiple cytotoxic agents as well as combination of interferon-α with anti-retroviral agents outside Japan.4(4) A standard salvage treatment has not yet been established except single agent mogamulizumab by prospective clinical trials,5(5) and thereby chemotherapy using multiple cytotoxic agents not contained in prior treatments has been used in practice.2(2) Due to the constitutive activation of NF-κB in ATL cells and its implications on oncogenesis as well as resistance to cytotoxic agents, the inhibition of NF-κB has been attracting interest as a possible target approach for the treatment of ATL.6(6)–8(8)

In the present study, we conducted a phase II clinical trial to investigate the efficacy and safety of bortezomib monotherapy based on its effects in vitro, in animal models, and in limited clinical settings.8(8)–12(12)

Materials and Methods

Study design and patients. This study was a multicenter, open-label, two-stage, single-arm, phase II study conducted in Japan (Clinical trial identifier UMIN000004061).

Eligibility criteria included age ≥20 years; histopathologically or cytologically confirmed acute-, lymphoma-type, or
chronic-type ATL with unfavorable prognostic factors, and further documented chemotherapy-refractory or -resistant disease after at least one line of treatment involving antineoplastic chemotherapeutics. Patients who relapsed after allogeneic hematopoietic stem cell transplantation were included. Other inclusion criteria comprised Eastern Cooperative Oncology Group (ECOG) performance status 0–2, ≥1 site of measurable disease with 1.5 cm ≥diameter or evaluable lesions in peripheral blood or skin, and adequate bone marrow, hepatic, renal, and cardiac function. Exclusion criteria included previous bortezomib treatments, the presence or history of interstitial lung disease or pulmonary fibrosis, peripheral neuropathy ≥ grade 2 or ≥ grade 1 with pain, invasion to the central nervous system, active infection including hepatitis B, C, and human immunodeficiency virus, or other serious and/or uncontrolled medical conditions. Patients with prior use of any investigational agents and anticancer therapy excluding daily oral etoposide and/or sobuzoxane for 4 weeks, and for 2 weeks in case of daily oral etoposide or sobuzoxane, before the study started were excluded.

This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines, applicable Japanese regulations, and the Declaration of Helsinki. The protocol and all amendments were reviewed and approved by the Institutional Review Board of each center. All patients provided written informed consent before enrolment.

**Procedures.** Patients were scheduled to receive intravenous bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 in eight 3-week cycles until disease progression per investigator review, unacceptable toxicity, death, or discontinuation for other reasons. Dose reductions and/or interruptions according to the study protocol were permitted for toxicity.

Computed tomography scans of the neck, chest, abdomen, and pelvis to evaluate radiological tumors were scheduled at screening, on day –7 to +1 of cycles 3, 5, and 7. Responses were also assessed at the end of the treatment or the day of abandoning the protocol treatment for any reason. Adverse events (AEs) were monitored continuously throughout the study and for 38 days after the last study drug dose or the day of initiation of subsequent treatments upon progression. A complete blood count (CBC) and serum chemistry were assessed at baseline, on the day of the treatment, and at the end of the treatment.

**Statistical analysis.** Efficacy and safety were assessed in all patients who received ≥1 dose of bortezomib. The primary endpoint was the overall response rate (ORR) assessed by the investigator, and secondary end points included safety, the best response by lesions, and progression-free survival (PFS). Objective responses were assessed according to the modified response criteria for ATL. AEIs and laboratory abnormalities were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0.

The two-stage design by the Southwest Oncology Group (SWOG) was adopted to permit early termination for futility. The targeted ORR was 25%; an ORR <5% precluded further investigations. Assuming a 5.5% significance level and 90% power, 15 patients were scheduled to receive the study treatment in the first stage. If no patient achieved responses, the study was scheduled to be terminated. Otherwise, 10 additional patients were planned to be enrolled and receive the treatment. If ≥4/25 enrolled patients developed a response, bortezomib was considered to be of clinical interest in this population.

### Table 1. Baseline patient demographics and disease histories

| Age, years | Median | Range |
|------------|--------|-------|
| 63.8       |        | 49-73 |

| Sex        | Male  | Female |
|------------|-------|--------|
|            | 10    | 5      |

| ECOG performance status | 0 | 1 | 2 |
|-------------------------|---|---|---|
|                         | 6 | 9 |

| Disease subtype at diagnosis | Acute | Lymphoma | Unfavorable chronic |
|------------------------------|-------|----------|--------------------|
|                              | 3     | 10       | 2                  |

| Prior treatment | Number of prior chemotherapy regimens |
|-----------------|--------------------------------------|
|                 | CHOP, CHOP-like                      |
|                 | VCAP-AMP-VECP                        |
|                 | Multi-agents other than above        |
|                 | VP-16                               |
|                 | VP-16 + sobuzoxane                  |
|                 | Mogamulizumab                       |
|                 | Sobuzoxane                          |
|                 | Lenalidomide                        |
|                 | Radiation                           |
|                 | Allogeneic stem cell transplantation |
|                 | 9                                    |
|                 | 6                                    |
|                 | 5                                    |
|                 | 4                                    |
|                 | 7                                    |

**Prior chemotherapy regimens**

- CHOP, combination chemotherapy consisting of vincristine (VCR), cyclophosphamide (CPM), doxorubicin (DOX), and prednisolone (PSL).
- VCAP-AMP-VECP, sequential combination chemotherapy consisting of VCAP (VCR, CPM, DOX, and PSL), AMP (DOX, ranimustine, and PSL), and VECP (vinodesine, etoposide, carboplatin, and PSL).

**Results**

Between August 2010 and November 2013, 15 patients were enrolled from five centers in Japan and received ≥1 bortezomib dose. Table 1 shows the baseline demographics and disease histories of these patients. At the time of the diagnosis for aggressive ATL, 3, 10, and 2 patients had the acute-, lymphoma-, and unfavorable chronic-type, respectively. Before enrollment, 14 patients received aggressive chemotherapy involving multiple agents and the other patient received multiple cycles of chemotherapy with the daily administration of etoposide with or without sobuzoxane. Moreover, three and one patients had a history of being treated with mogamulizumab and lenalidomide, respectively. Nine patients relapsed after chemotherapy, and six patients were refractory to multi-agent aggressive chemotherapy including a patient who relapsed after allogeneic hematopoietic stem cell transplantation.

At the time of the analysis after the completion of stage 1, all patients discontinued the treatment due to disease progression (n = 11), AEs (n = 3), and by the patient’s request due to anxiety to participate in the clinical trial (n = 1). The AEs that resulted in discontinuation were two cases of peripheral neuropathy and one of hyponatremia. The median bortezomib treatment duration was 25 (8 to 106) days. The best overall
responses were PR in one patient and SD in five patients, resulting in 6.7% for ORR (95% confidence interval (CI) 0.17-31.95%). Responses according to disease sites were one CR in peripheral blood, two PR in measurable targeted lesions with percentage reductions in the sum of the products of the greatest diameters (SPD): 87.1% and 61.3%; and two PR in skin lesions. In two patients who achieved SD in measurable targeted lesions, their percentage reductions in SPD were 49.6% and 46.7%. PFS was 38.0 (95% CI; 18.0–106.0) days. An unplanned analysis of PFS in patients who achieved more than SD (n = 6) and received more than one cycle of the treatment (n = 6) was 106 (95% CI; 60–122) days and 49 (95% CI; 25–106) days, respectively (Table 2). All patients developed ≥1 AEs. AEs occurring in ≥20% of patients regardless of the relationship to the study drug were shown in Table 3. Grade 3/4 drug-related AEs occurred in 12 patients, and included thrombocytopenia (n = 7), leukopenia (n = 2), lymphopenia (n = 3), peripheral neuropathy (n = 2), anemia (n = 1), neutropenia (n = 1), constipation (n = 1), ileus (n = 1), fever (n = 1), bacterial pneumonia (n = 1), elevations in lactate dehydrogenase (LDH) (n = 1), gamma-glutamyl transpeptidase (γ-GTP) (n = 1), or C-reactive protein (CRP) (n = 1), hypotension (n = 1), syncope (n = 1), presyncope (n = 1), and acute renal failure (n = 1). Of these, acute renal failure, which was transient and accompanied by elevations in uric acid and potassium, was considered to be tumor lysis syndrome. Among them, six serious AEs were observed in five patients. Those were syncope, presyncope, ileus, peripheral neuropathy, and hypotension. Syncope was considered to be mainly related to concomitant medications, and presyncope was related to severe diarrhea by the irinotecan which was applied for the next treatment after the cessation of the trial. Another serious AE was the reactivation of hepatitis virus type B; a patient who was positive HBe-Ag with undetectable HBV-DNA by polymerase chain reaction (PCR) at the time of enrollment became detectable HBV-DNA by PCR without any serological evidence of hepatic injury. There were no deaths during this trial. It fulfilled the planned settings to proceed to the second stage since one patient acquired PR in the first stage; however, the coordinating committee decided to terminate this study because single agent activity did not appear to be very promising for this cohort of patients in consideration to the changing circumstances by the introduction of a novel anti-CC chemokine receptor 4 (CCR4) monoclonal antibody mogamulizumab.5)

Discussion

This study is the first prospective clinical trial of bortezomib for the treatment of ATL. Bortezomib induced PR and SD in one and five patients, respectively. These results did not comply with the <1 response out of 15 patients to declare the ineffectiveness of this drug to the targeted cohort of patients in the first stage; however, the coordinating committee decided to

Table 2. Patient characteristics and summary of responses

| Case | Sex | Age (years) | Disease status | No. prior treatment regimens | Response to prior therapy | No. doses treated | Reasons for termination | Response | Measurable targeted lesions | PFS (Days) |
|------|-----|-------------|----------------|----------------------------|--------------------------|-------------------|------------------------|----------|---------------------------|------------|
| 1    | M   | 49          | Refractory     | 2                          | PD                       | 3                 | AE                     | PR       | –                         | 122        |
| 2    | F   | 70          | Relapsed       | 2                          | PR                       | 18                | PD                     | SD       | –                         | 106       |
| 3    | M   | 56          | Relapsed       | 1                          | SD                       | 16                | PD                     | SD       | –                         | 106       |
| 4    | M   | 56          | Relapsed       | 2                          | CR                       | 12                | PD                     | SD       | CR                       | 60        |
| 5    | F   | 68          | Relapsed       | 2                          | PR                       | 4                 | AE                     | SD       | –                         | 48†       |
| 6    | M   | 67          | Refractory     | 3                          | PD                       | 8                 | PD                     | SD       | –                         | 38        |
| 7    | M   | 62          | Relapsed       | 1                          | CR                       | 7                 | PD                     | PD       | –                         | 38        |
| 8    | M   | 54          | Relapsed       | 4                          | SD                       | 4                 | AE                     | PR       | –                         | 36†       |
| 9    | F   | 70          | Relapsed       | 1                          | PR                       | 5                 | PD                     | –        | PD                       | 25        |
| 10   | M   | 69          | Refractory     | 2                          | PD                       | 4                 | PD                     | SD       | –                         | 25        |
| 11   | M   | 63          | Relapsed       | 7                          | PD                       | 4                 | PD                     | PD       | –                         | 18        |
| 12   | F   | 69          | Refractory     | 2                          | PD                       | 4                 | PD                     | SD       | –                         | 17        |
| 13   | F   | 63          | Relapsed       | 1                          | CR                       | 4                 | PD                     | –        | PD                       | 14        |
| 14   | M   | 73          | Refractory     | 2                          | PD                       | 3                 | PD                     | SD       | –                         | 11        |
| 15   | M   | 68          | Relapsed       | 1                          | CR                       | 2                 | Others                 | NE       | –                         | 8         |

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate; PFS, progression-free survival; NE, not evaluable. *censored.

Table 3. Adverse events occurring in ≥20% of patients regardless of the relationship to the study drug

| Events                          | Total n = 15, n (%) |
|--------------------------------|---------------------|
|                                | All Grades | Grade 3/4 |
| Non-hematological              |           |           |
| Fever                          | 7 (46.7)   | 1 (6.7)   |
| Anorxia                        | 6 (40.0)   | 0         |
| Constipation                   | 4 (26.7)   | 1 (6.7)   |
| Diarrhea                       | 4 (26.7)   | 0         |
| Fatigue                        | 4 (26.7)   | 0         |
| Peripheral neuropathy          | 4 (26.7)   | 2 (13.3)  |
| Decrease in IgG                | 4 (26.7)   | 0         |
| Decrease in IgM                | 4 (26.7)   | 0         |
| Decrease in IgA                | 3 (20.0)   | 0         |
| Hematological                  |           |           |
| Thrombocytopenia               | 11 (73.3)  | 7 (46.7)  |
| Leukopenia                     | 5 (33.3)   | 2 (13.3)  |
| Lymphopenia                    | 5 (33.3)   | 3 (20.0)  |
| Anemia                         | 4 (26.7)   | 1 (6.7)   |

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate; PFS, progression-free survival; NE, not evaluable. *censored.
terminate this study because single agent activity did not appear to be very promising for this cohort of patients. Bortezomib demonstrated acceptable tolerability in this population with no new safety findings. The toxicities observed were similar to those commonly observed in patients with multiple myeloma, and the incidence of peripheral neuropathy was not elevated in spite of the use of vincristine during prior chemotherapy regimens in most patients.

Relapsed and refractory aggressive ATL frequently shows rapid progression; five out of 15 patients could not receive more than one cycle of bortezomib due to progression. The duration of the treatment may have been too short to evaluate its efficacy in these patients because the median time to the first response was previously reported to be 1.3 months in a clinical trial on bortezomib in patients with relapsed or refractory mantle cell lymphoma. (14)

Several prospective clinical trials elucidating the efficacy of single agent activity have been performed on patients with ATL. A phase I/II study of sobuzoxane showed two CR and eight PR in 23 evaluable patients including 17 treatment-naïve, and two chronic-type. (15) A phase II study of imidotecan showed one CR and four PR in 13 evaluable relapsed or refractory patients. (16) A phase II study of cladribine showed one PR in 15 evaluable relapsed or refractory patients. (17) Mogamulizumab recently showed eight CR and six PR in 26 evaluable relapsed ATL patients in a Phase II study. (18) It is impossible to compare the findings of independent clinical trials, and the nature of heterogeneity in the clinical features of ATL makes it more difficult to compare the activities of study drugs. In spite of these facts, the single agent activity of bortezomib was not considered to be promising enough to proceed to further studies.

A randomized phase III study of frontline rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib-R-CHOP (VR-CHOP) in mantle cell lymphoma recently revealed the significantly superior PFS, CR/CRu rate, and time to progression in a VR-CHOP arm. (18) However, a similarly designed phase II trial for the non-germinal center B-cell subtype of diffuse large cell lymphoma failed to show differences in CR rates and overall response rates (https://clinicaltrials.gov/ct2/show/results/NCT01040871?term=VR-CAP&rank=1). No information is currently available to explain the differences in these diverse findings from the viewpoint of the molecular pathophysiology of the diseases and the mechanisms underlying the actions of bortezomib. Our results suggest that ATL cells may not be reliant on NF-κB for their survival, at least in some populations of refractory/resistant ATL patients, and/or the inhibition of NF-κB was not achieved in ATL cells in humans by administering a conventional dose of bortezomib. (19)

In conclusion, bortezomib monotherapy demonstrated definitive signs of activity in patients with heavily-treated relapsed and refractory ATL; however, its overall efficacy was not sufficiently promising. Future studies in combination with cytotoxic agents or other targeted therapies are warranted.

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