Cancer Science
Japanese Cancer Association JCA
Open Access

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

Kenji Ishitsuka,[1] Atae Utsunomiya,[2] Hiroo Katsuya,[1] Shogo Takeuchi,[2] Yoshifusa Takatsuka,[2] Michihiro Hidaka,[3] Tatsunori Sakai,[3] Makoto Yoshimitsu,[4] Takashi Ishida[5] and Kazuo Tamura[1]

[1]Division of Oncology, Hematology and Infectious Diseases, Fukuoka University, Fukuoka; [2]Department of Hematology, Imamura Bun-in Hospital, Kagoshima; [3]Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto; [4]Division of Hematology and Immunology, Center for Chronic Viral Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima; [5]Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Key words

Adult T-cell leukemia/lymphoma, bortezomib, nuclear factor-κB, proteasome inhibitor, salvage treatment

Correspondence

Kenji Ishitsuka, Division of Oncology, Hematology and Infectious Diseases, Fukuoka University, 7-45-1 Nanakuma, Jonan, Fukuoka 814-0180, Japan. Tel: +81-92-801-1011; Fax: +81-92-865-5656; E-mail kenjiishitsuka@fukuoka-u.ac.jp

Clinical trial identifier: UMIN000004061.

Funding information

This study was supported by a Health Labour Sciences Research Grant for Clinical Research (H23-rinkensui-ippan-011 and H26-kakushintekigann-ippan-136) from the Ministry of Health, Labour and Welfare (Japan), by the Practical Research for Innovative Cancer Control from Japan Agency for Medical Research and Development, AMED, and Clinical Hematology Oncology Treatment Study Group (Fukuoka, Japan) (K.I.). The study drug was supplied by Janssen, Japan (Tokyo, Japan).

Received April 22, 2015; Revised June 23, 2015; Accepted July 4, 2015

Cancer Sci **106** (2015) 1219–1223

doi: 10.1111/cas.12735

Adult T-cell leukemia/lymphoma (ATL) is a malignancy of peripheral T-lymphocytes with a poor prognosis. This multicenter, two-stage, single-arm, phase II study assessed the efficacy and safety of bortezomib in patients with relapsed/refractory ATL who received at least one regimen of chemotherapy. The primary endpoint was the best overall response rate (ORR), and secondary endpoints included safety, the best response by lesions, and progression-free survival (PFS). Fifteen patients were enrolled in the first stage of this study. One partial remission (PR) and five stable disease (SD) were observed as the best overall responses, and ORR was 6.7% (95% confidence interval (C.I.) 0.17-31.95%). Responses according to disease sites were one complete remission (CR) in peripheral blood, two PR in measurable targeted lesions, and two PR in skin lesions. Progression-free survival (PFS) was 38 (95% CI; 18–106) days. All patients developed ≥1 adverse events (AEs), and 80% of patients had ≥1 grade 3/4 AEs; however, no new safety findings were obtained. Although these results fulfilled the planned settings to proceed to the second stage, the coordinating committee decided to terminate this study because single agent activity did not appear to be very promising for this cohort of patients.

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]

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] Adult T-cell leukemia/lymphoma has been divided into four clinical subtypes; acute-, lymphoma-, chronic-, and smoldering-types.[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] A standard salvage treatment has not yet been established except single agent mogamulizumab by prospective clinical trials,[5] and thereby chemotherapy using multiple cytotoxic agents not contained in prior treatments has been used in practice.[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 targeted approach for the treatment of ATL.[6–8]

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.[8–12]

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/m^2 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.[4] AEs 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.[13] 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	63.8
Range	49–73
Sex	
Male	10
Female	5
ECOG performance status	
0	6
1	9
Disease subtype at diagnosis	
Acute	3
Lymphoma	10
Unfavorable chronic	2
Prior treatment	
Number of prior chemotherapy regimens	
1	5
2	7
3	1
4	1
7	1
Prior chemotherapy regimens	
CHOP, CHOP-like	9
VCAP-AMP-VECP	6
Multi-agents other than above	5
VP-16	6
VP-16 + sobuzoxane	3
Mogamulizumab	3
Sobuzoxane	1
Lenalidomide	1
Radiation	2
Allogeneic stem cell transplantation	1

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

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				PFS (Days)
								Measurable targeted lesions	PB	Skin	ORR	
1	M	49	Refractory	2	PD	3	AE	PR	–	–	PR	122
2	F	70	Relapsed	2	PR	18	PD	SD		–	SD	106
3	M	56	Relapsed	1	SD	16	PD	SD	–	–	SD	106
4	M	56	Relapsed	2	CR	12	PD	SD	CR	SD	SD	60
5	F	68	Relapsed	2	PR	4	AE	SD	–	–	SD	48†
6	M	67	Refractory	3	PD	8	PD	SD		–	PD	38
7	M	62	Relapsed	1	CR	7	PD	PD	–	PR	PD	38
8	M	54	Relapsed	4	SD	4	AE	PR	–	SD	SD	36†
9	F	70	Relapsed	1	PR	5	PD	–	PD	PR	PD	25
10	M	69	Refractory	2	PD	4	PD	SD	–	–	PD	25
11	M	63	Refractory	7	PD	4	PD	PD	SD	–	PD	18
12	F	69	Refractory	2	PD	4	PD	SD	–	SD	PD	17
13	F	63	Relapsed	1	CR	4	PD	PD	–	–	PD	14
14	M	73	Refractory	2	PD	3	PD	SD	SD	PD	PD	11
15	M	68	Relapsed	1	CR	2	Others	NE	–	–	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.

responses were PR in one patient and SD in five patients, resulting in 6.7% for ORR (95% confidence interval (C.I.) 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), hyponatremia (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 hyponatremia. 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 HBc-Ab 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 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)
Anorexia	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)

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 irinotecan 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.[5] 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-CAP (VR-CAP) in mantle cell lymphoma recently revealed the significantly superior PFS, CR/CRu rate, and time to progression in a VR-CAP 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 administrating 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.

Acknowledgments

This study was funded by a Health Labour Sciences Research Grant for Clinical Research (H23-rinkensui-ippan-011 and H26-kakushintekigann-ippan-136) from the Ministry of Health, Labour and Welfare (Japan), by the Practical Research for Innovative Cancer Control from Japan Agency for Medical Research and Development, AMED, and Clinical Hematology Oncology Treatment Study Group (Fukuoka, Japan) (K.I.). The study drug was supplied by Janssen, Japan (Tokyo, Japan). The authors thank all of the patients who participated in this study. We also thank the Independent Data Monitoring Committee: Drs Takeharu Yamanaka (Yokohama City University, Yokohama, Japan), Kisato Nosaka (Kumamoto University, Kumamoto, Japan), Ilseung Choi (National Hospital Organization Kyusyu Cancer Center, Fukuoka, Japan), and Masaki Fujita (Fukuoka University, Fukuoka, Japan); and Dr Keita Noda, Kenji Yamaguchi, and Shin Kobayashi (Fukuoka University, Fukuoka, Japan) for their trial support.

Disclosure Statement

A. Utsunomiya received honoria from Kyowa Hakko Kirin Co., Ltd., and T. Ishida received research grants from Bayer, Celgene, and Kyowa Hakko Kirin, Co., Ltd., and honoria from Kyowa Hakko Kirin, Co., Ltd. This study was designed by the coordinating committee which was independent from any pharmaceutical companies. Supply of drugs for experiments: Bortezomib was provided by Janssen, Japan (Tokyo, Japan). Support provided to collect/analyze data or to write the manuscript: The collection and analysis of the data as well as the interpretation of the study were performed independently from Janssen, Japan. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

References

1 Hideshima T, Chauhan D, Richardson P *et al.* NF-kappa B as a therapeutic target in multiple myeloma. *J Biol Chem* 2002; **277**: 16639–47.
2 Ishitsuka K, Tamura K. Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma. *Lancet Oncol* 2014; **15**: e517–26.
3 Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). *Br J Haematol* 1991; **79**: 428–37.
4 Tsukasaki K, Hermine O, Bazarbachi A *et al.* Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. *J Clin Oncol* 2009; **27**: 453–9.
5 Ishida T, Joh T, Uike N *et al.* Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol* 2012; **30**: 837–42.
6 Ballard DW, Bohnlein E, Lowenthal JW, Wano Y, Franza BR, Greene WC. HTLV-I tax induces cellular proteins that activate the kappa B element in the IL-2 receptor alpha gene. *Science* 1988; **241**: 1652–5.
7 Mori N, Fujii M, Ikeda S *et al.* Constitutive activation of NF-kappaB in primary adult T-cell leukemia cells. *Blood* 1999; **93**: 2360–8.
8 Tan C, Waldmann TA. Proteasome inhibitor PS-341, a potential therapeutic agent for adult T-cell leukemia. *Cancer Res* 2002; **62**: 1083–6.
9 Satou Y, Nosaka K, Koya Y, Yasunaga JI, Toyokuni S, Matsuoka M. Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro. *Leukemia* 2004; **18**: 1357–63.
10 Nasr R, El-Sabban ME, Karam JA *et al.* Efficacy and mechanism of action of the proteasome inhibitor PS-341 in T-cell lymphomas and HTLV-I associated adult T-cell leukemia/lymphoma. *Oncogene* 2005; **24**: 419–30.
11 Shu ST, Nadella MV, Dirksen WP *et al.* A novel bioluminescent mouse model and effective therapy for adult T-cell leukemia/lymphoma. *Cancer Res* 2007; **67**: 11859–66.
12 Pise-Masison CA, Radonovich M, Dohoney K *et al.* Gene expression profiling of ATL patients: compilation of disease-related genes and evidence for TCF4 involvement in BIRC5 gene expression and cell viability. *Blood* 2009; **113**: 4016–26.
13 Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. *Stat Med* 1992; **11**: 853–62.
14 Fisher RI, Bernstein SH, Kahl BS *et al.* Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2006; **24**: 4867–74.
15 Ohno R, Masaoka T, Shirakawa S *et al.* Treatment of adult T-cell leukemia /lymphoma with MST-16, a new oral antitumor drug and a derivative of bis (2,6-dioxopiperazine). The MST-16 Study Group. *Cancer* 1993; **71**: 2217–21.
16 Tsuda H, Takatsuki K, Ohno R *et al.* Treatment of adult T-cell leukaemia-lymphoma with irinotecan hydrochloride (CPT-11). CPT-11 Study Group on Hematological Malignancy. *Br J Cancer* 1994; **70**: 771–4.

17 Tobinai K, Uike N, Saburi Y *et al.* Phase II study of cladribine (2-chlorodeoxyadenosine) in relapsed or refractory adult T-cell leukemia-lymphoma. *Int J Hematol* 2003; **77**: 512–17.
18 Robak T, Huang H, Jin J *et al.* Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *N Engl J Med* 2015; **372**: 944–53.
19 Chaturvedi MM, Sung B, Yadav VR, Kannappan R, Aggarwal BB. NF-kappaB addiction and its role in cancer: 'one size does not fit all'. *Oncogene* 2011; **30**: 1615–30.