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ORIGINAL REPORT

Phase II Clinical Experience With the Novel Proteasome Inhibitor Bortezomib in Patients With Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma

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ABSTRACT

Purpose
To determine the antitumor activity of the novel proteasome inhibitor bortezomib in patients with indolent and mantle-cell lymphoma (MCL).

Patients and Methods
Patients with indolent and MCL were eligible. Bortezomib was given at a dose of 1.5 mg/m^2 on days 1, 4, 8, and 11. Patients were required to have received no more than three prior chemotherapy regimens, with at least 1 month since the prior treatment, 3 months from prior rituximab, and 7 days from prior corticosteroids; absolute neutrophil count more than 1,500/μL (500/μL if documented bone marrow involvement); and platelet count more than 50,000/μL.

Results
Twenty-six patients were registered, of whom 24 were assessable. Ten patients had follicular lymphoma, 11 had MCL, three had small lymphocytic lymphoma (SLL) or chronic lymphocytic leukemia (CLL), and two had marginal zone lymphoma. The overall response rate was 58%, with one complete remission (CR), one unconfirmed CR (CRu), and four partial remissions (PR) among patients with follicular non-Hodgkin's lymphoma (NHL). All responses were durable, lasting from 3 to 24+ months. One patient with MCL achieved a CRu, four achieved a PR, and four had stable disease. One patient with MCL maintained his remission for 19 months. Both patients with marginal zone lymphoma achieved PR lasting 8+ and 11+ months, respectively. Patients with SLL or CLL have yet to respond. Overall, the drug was well tolerated, with only one grade 4 toxicity (hyponatremia). The most common grade 3 toxicities were lymphopenia (n = 14) and thrombocytopenia (n = 7).

Conclusion
These data suggest that bortezomib was well tolerated and has significant single-agent activity in patients with certain subtypes of NHL.

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INTRODUCTION

The ubiquitin-proteasome pathway plays an essential role in the degradation of most short- and long-lived intracellular proteins in eukaryotic cells.[1] At the heart of this degradative pathway is the 26S proteasome, an adenosine triphosphate–dependent, multicatalytic protease. Some of the proteins degraded by the ubiquitin-proteasome pathway include p53, p21, p27, nuclear factor kappa B (NF-κB), and bcl-2.[1-4] Preclinical observations have suggested that inhibitors of this pathway act through multiple mechanisms to arrest tumor growth, induce cell death, and inhibit tumor metastasis and angiogenesis.[5-8] Phase I trials have confirmed that bortezomib is well tolerated

and may have potential clinical activity in patients with select lymphomas.[9,10]

The ubiquitin-proteasome pathway plays a critical role in regulating cell cycle control.[4] For example, cyclins, cyclin-dependent kinases (cdk), and cdk inhibitors (p21, $p27^{kip1}$) are temporally degraded during the cell cycle by the ubiquitin-proteasome pathway. Both p21 and p27 can induce cell cycle arrest by inhibiting cdk.[11] The ordered degradation of these proteins is required for progression through cell cycle and mitosis. Another target of the ubiquitin-proteasome pathway is the tumor suppressor p53, which acts as a negative regulator of cell growth. p53 is required for the transcription of a number of genes involved in cell cycle control and DNA synthesis, and also plays an important function in apoptosis induced by cellular damage, including ionizing radiation.[11]

In addition to the regulation of cell cycle control, the ubiquitin-proteasome pathway plays an important role in modulating the important transcription factor NF-κB. NF-κB is responsible for the activation of several genes that contribute to the malignant phenotype, including genes that promote cell proliferation, cytokine release, antiapoptosis, and changes in cell surface adhesion molecules. The activity of NF-κB is tightly regulated by the ubiquitin-proteasome pathway through the accumulation or degradation of IκB, which binds to and inactivates NF-κB.[4,12] Cell adhesion molecules (CAMs), such as E-selectin, ICAM-1, and VCAM-1, are proteins regulated by NF-κB and are involved in tumor metastasis and angiogenesis in vivo.[13] As such, tumor cell metastasis may well be prevented through the downregulation of NF-κB–dependent CAM expression. NF-κB also controls cell viability by regulating both anti- and proapoptotic proteins in the mitochondrial membrane.[14] Several lines of preclinical evidence now suggest that inhibiting NF-κB activation by stabilizing the IκB protein can render cells more sensitive to environmental stress and cytotoxic agents, ultimately leading to programmed cell death. In addition, many lines of experimental investigation have shown that inhibition of the proteasome, and perhaps even NF-κB, sensitizes cells to a host of conventional cytotoxic therapies.[1,5,7]

Although dysregulation of NF-κB is common to many malignancies, select lymphoproliferative malignancies are often characterized by pathognomonic molecular lesions, which may render them especially vulnerable to inhibitors of this pathway. Specific lesions include the following examples. First, the constitutive overexpression of cyclin D1 (bcl-1, PRAD1) in mantle-cell lymphoma (MCL) is due to the t(11;14)(q13;q32) translocation, which may also be augmented through the constitutive activation of NF-κB (and AP-1), which has been shown in cell lines of MCL.[15] Second, the constitutive overexpression of the antiapoptotic protein bcl-2 in follicular lymphoma due to the t(14;18)(q32;q21) translocation can be mitigated through the inhibition of the 26S proteasome,[16,17] which may be attributed in part to inactivated NF-κB. Third, the constitutive overexpression of NF-κB is noted in gene array studies of chemotherapy-refractory diffuse large B-cell neoplasms (ie, ABC or activated B-cell lymphomas).[18,19] Fourth, the t(1:14)(p22:q32) translocation leading to expression of the bcl-10 gene in mucosa-associated lymphoid tissue lymphomas is believed to involve a caspase recruitment domain–containing protein that activates NF-κB.[20,21]

Bortezomib (Velcade, formerly known as PS-341; Millenium Pharmaceuticals, Cambridge, MA) is a dipeptidyl boronic acid inhibitor with high specificity for the 26S proteasome.[22] It is the first member of this new class of antitumor agents to be studied in human clinical trials, leading recently to its approval by the US Food and Drug Administration for the treatment of relapsed or refractory multiple myeloma. Phase I and II clinical studies have demonstrated that bortezomib is a well-tolerated agent with minimal hematologic toxicity. In addition, it has been shown that bortezomib is capable of producing a dose-related effect on proteasome inhibition when analyzed 1 hour postinfusion, with little interpatient variability.[9,10] We present here the first clinical experience of bortezomib in patients with indolent and mantle cell non-Hodgkin's lymphoma (NHL).

PATIENTS AND METHODS

Patient Selection

Patients were required to have histologically confirmed lymphoma according to the WHO/Revised European-American Lymphoma classification, including chronic lymphocytic leukemia (CLL); B-cell small lymphocytic lymphoma (SLL); marginal zone lymphoma; follicular lymphoma, grades 1, 2, or 3; MCL; and Waldenström's macroglobulinemia. Prior history of transformed lymphoma was permitted as long as recent biopsies revealed no evidence of aggressive lymphoma. Patients had to meet the following eligibility requirements for enrollment onto the study. Patients had to have measurable disease (defined as $\geq$ 1 cm with spiral computed tomography scan); for patients with leukemic forms of NHL, including CLL, patients had to have an absolute lymphocytosis more than 5×10^9/L with a B-cell phenotype ($CD19^+$, $CD20^+$, or $CD23^+$), and more than 30% bone marrow lymphocytes. Patients had to have received no more than three prior lines of conventional cytotoxic therapy, and were required to have stopped receiving cytotoxic chemotherapy for at least 4 weeks before study enrollment (6 weeks for bischloroethylnitrosourea or mitomycin, and at least 7 days must have elapsed since the use of corticosteroids). There had to be a period of at least 3 months since the last administration of any monoclonal antibody. Patients had to be 18 years of age or older, have a life expectancy of 3 months or greater, and have a Karnofsky performance status more than 60%. Patients could have no signs of congestive heart failure according the New York Heart Failure Guidelines Class III/IV. Patients were allowed febrile episodes up to 38.5°C as long as there was no evidence of active infection. Patients were also eligible only if they had at baseline a grade 1 or less sensory neuropathy. The protocol

was approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board, and all patients were required to sign an informed consent approved by the Institutional Review Board.

In addition, patients were required to meet the following criteria within 2 days of study drug administration: an absolute neutrophil count $\geq$ 1,500/μL (if known lymphomatous involvement of the bone marrow, then absolute neutrophil count $>$ 500/mL); a platelet count of $\geq$ 50,000/μL for the first dose of every cycle, and more than 30,000/μl for doses delivered on days 4, 8, and 11; a total bilirubin $\leq$ 1.5$\times$ upper institutional limit of normal (ULN); an AST and ALT $\leq$ 2.5$\times$ ULN (4$\times$ ULN if the patient had liver involvement); and a creatinine $\leq$ 1.5$\times$ ULN. Initially, patients were required to have a platelet count $\geq$ 100,000/μL, but these criteria were modified downward given the absence of bleeding complications and the realization that many patients were unnecessarily missing doses secondary to the high cutoff value. Patients were excluded if they were pregnant; had evidence of intracranial disease; had major surgery within 4 weeks of study drug administration; had uncontrolled illness including active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, a myocardial infarction, or cerebrovascular accident within 6 months of study enrollment; had known HIV disease; or had a psychiatric illness that would limit compliance with study requirements.

Study Design

This was a single-center, single-agent phase II study of bortezomib in patients with relapsed, refractory, or untreated indolent NHL and MCL. The major objectives of the study were to determine the frequency and duration of complete and partial response for patients with indolent lymphoproliferative disorders treated with bortezomib. The study used a Simon two-stage design. Initially, 18 patients were enrolled onto the first stage. If no more than two patients responded, the trial would have been terminated. If at least three patients responded, then up to 35 patients could be enrolled. These statistics were predicated on the assumption that should 20% of patients respond, the drug will be declared as having promising activity.

Drug Administration

Bortezomib (*N*-pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid; CAS No. 179324-69-7) was supplied to investigators by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. Bortezomib for injection was supplied as a lyophilized powder for reconstitution. Each vial contained 3.5 mg of bortezomib and 35 mg mannitol United States Pharmacopeia. Each vial was reconstituted with 3.5 mL normal (0.9%) saline, such that the reconstituted solution contained bortezomib at a concentration of 1 mg/mL. The pH of the reconstituted solution was between 5 and 6. The drug was injected during 3 to 5 seconds into a side arm of a running intravenous infusion of normal saline at 100 mL/h. At the end of the drug infusion, 10 mL of normal saline was infused to flush the line. There was no upper limit on planned therapy, and patients could continue to receive drug as long as there was evidence of clinical benefit without excess toxicity.

Dose Modification

Patients were treated at a dose of 1.5 mg/m^2 twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 1-week rest period (one cycle). Treatment was delayed for patients whose peripheral blood counts failed to meet the eligibility criteria for re-treatment, and they were re-treated once their counts recovered. Use of antiemetics, erythropoietin, and filgrastim was allowed if deemed necessary by the treating physician. Their use was dictated by standard institutional guidelines. Although rare, in most patients in whom an antiemetic was required, a single oral dose of granisetron was administered.

In patients who developed a grade 3 or 4 nonhematologic toxicity of any sort or grade 4 neutropenic fever or thrombocytopenia, the dose was reduced to 1.3 mg/m^2, and then to 1.1 mg/m^2 for a repeat episode of toxicity. Patients who experienced persistent nonhematologic toxicity despite this dose reduction were removed from the study. Treatment was delayed until these toxicities resolved to baseline. Dose reductions were also allowed for patients who developed asthenia, anorexia, or neuropathy of any grade, which in the judgment of the treating physician, was believed to be clinically significant and detrimental to the patients' continued involvement on study.

Response Criteria

Response criteria for patients enrolled onto the study followed the guidelines previously reported by Cheson et al.[23] All responses were characterized as either complete remission (CR), unconfirmed complete remission (CRu), partial remission (PR), stable disease (SD), or progression of disease (POD). Response criteria for patients with leukemic forms of NHL, including CLL, followed the National Cancer Institute guidelines previously reported by Cheson et al.[24] Response was routinely assessed after every two cycles. For patients removed from the study, a 1-month confirmatory scan was performed, and patients were then restaged every 3 months. There was no upper limit on the amount of bortezomib any patient could receive. In general, patients continued participating in the study until one of the following criteria were met: the patient withdrew consent or the patient experienced unacceptable toxicity. If the patient achieved a PR, therapy continued until maximal benefit; if the patient achieved a CR, the patient continued for two cycles beyond CR.

Nerve Conduction Studies

Electrodiagnostic evaluations, including nerve conduction studies and needle electromyography, were completed on select patients. Motor and sensory nerve conduction and needle electromyographic studies were performed and responses recorded using standardized equipment and techniques. Needle electromyography was performed on selected muscles of the upper and or lower extremity and their corresponding paraspinal muscles. Interpretation of the completed electrodiagnostic studies was done by a board-certified electromyographer.

RESULTS

Demographics

This study reports on our initial experience of 26 consecutive patients enrolled between June 2001 and December of 2003. Table 1 presents the demographic and clinical features of all study patients. Twenty-six patients were registered for treatment, of whom 24 were assessable for response (ie, they completed at least two cycles of therapy). All patients were assessable for toxicity. One of the two inassessable patients had a history of follicular lymphoma and received two dose of bortezomib, which was followed by a

Table 1. Patient Demographics

Characteristic	No. of Patients	%
No. of patients	26	
Male	14	54
Female	12	46
White non-Hispanic	24	92
African American or Hispanic	2	8
Age, years		
Median	63	
Range	44–78	
Disease		
Follicular lymphoma, grade	10	38
I	4	15
II	4	15
III	2	8
Mantle cell lymphoma	11	42
Small lymphocytic	3	12
Lymphoma or CLL		
Marginal zone lymphoma	2	8
Prior treatment		
Median number of prior therapies* (all)	3	
Median number of prior cytotoxic therapies	3	
Alkylator-based therapy		
CHOP	12	48
R-CHOP	5	19
CVP	5	20
R-ICE	2	8
ICE	1	4
EPOCH	1	4
ESHAP	1	4
BACOP or CHOEP	1	4
Oral CTX	1	4
Chlorambucil	1	4
HDC + ASCT	3	12
Purine analog–based therapy		
Fludarabine	1	4
CyFlu	2	10
2-Chlorodeoxyadenosine	1	4
Biological- or experimental-based therapy		
Rituximab alone	21	84
Zevalin	1	4
Bexxar	1	4
PEG interferon/ribavarin	1	4
Anti-B1 MAB	1	4
PDX	1	4
Radiation therapy	9	36
No prior treatment	1	4

Abbreviations: CLL, chronic lymphocytic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, CHOP plus rituximab; CVP, cyclophosphamide, vincristine, prednisone; R-ICE, ICE plus rituximab; ICE, ifosfamide, carboplatin, etoposide; EPOCH, etoposide, prednisone, vincristine; ESHAP, etoposide, methylprednisone, high-dose cytarabine, cisplatin; BACOP, bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone; CHOEP, CHOP plus etoposide; CTX, cytoxan; HDC, high-dose chemotherapy; ASCT, autologous stem-cell transplantation; PEG, polyethylene glycol; MAB, monoclonal antibody; PDX, 10-propargyl-10-deazaaminopterin (novel antifolate).

*Cytotoxic therapies include all chemotherapy-based treatment programs, radiation, and radioimmunotherapies, and excludes all biologically based treatments including rituximab- and interferon-based treatments.

thrombocytopenia with platelet counts ranging between 60,000 and 95,000/mL. This toxicity persisted for 2 weeks, which per the earlier versions of the study rendered him ineligible to be re-treated. As discussed, the platelet requirements were downgraded in subsequent amendments to the study. The second ineligible patient had a history of MCL with extensive gastrointestinal involvement. After several doses of bortezomib, he developed a grade 3 diarrhea with a documented *Clostridium difficile* infection that did not resolve during a 2-week period of observation and treatment, rendering him ineligible for treatment on study. A follow-up computed tomography scan of the abdomen and pelvis revealed marked progression of his disease.

There was a roughly even distribution in sex (54% male patients), with an unintended bias toward a largely white non-Hispanic population (92%). The median age of 63 years approximates the median age for patients with indolent lymphomas in general. The indolent lymphomas represent a vast diversity of biology and different disease subtypes, most of which are represented in this population. Approximately one third of all patients had follicular lymphoma (38%), including grades 1 to 3. Eleven patients (42%) had MCL, whereas three patients (12%) had SLL and two patients (8%) had marginal zone lymphoma. The median number of all prior therapies was three (range, 0 to 5), whereas the median number of prior cytotoxic chemotherapy regimens was also three (range, 0 to 3). All patients (with the exception of the one patient with no history of prior treatment) had been treated with at least one form of an alkylator-based treatment program, whereas only 15% received a purine analog–based regimen. Three patients had undergone prior peripheral-blood stem cell transplantation, and two had received prior radioimmunotherapy (tositumomab and iodine-131 tositumomab or yttrium-90 ibritumomab tiuxetan). These patients did not seem to exhibit any more toxicity than that of other patients participating in the study, and in fact, two of the five attained major remissions (CRu and PR). Fifteen of the 26 patients received prior rituximab as a single agent, with five of those patients receiving two or more courses of antibody therapy. Nine (35%) patients received prior radiotherapy. Only one patient was registered to the study who had received no prior therapy of any sort.

Dose Modifications

In general, the treatment was well tolerated. For the 26 registered patients, a total of 103 cycles of bortezomib were administered, which included 378 doses of the drug. The average number of cycles and doses received per patient was approximately four and 14.5, respectively. There was no difference in the amount of therapy administered to responders or nonresponders (4.2 *v* 4.3 cycles/patient and 16.3 *v* 15 doses per patient for responders and nonresponders, respectively). Thirteen patients (50%) missed at least one dose of drug. Among these patients, the median number of doses missed was four. The most common reason for a missed dose was thrombocytopenia, and the bulk

of these missed doses occurred early in the study, when the more stringent platelet count requirements were in place (ie, $\geq$ 100,000/μL). After the modification to platelet count requirements, there have been no missed doses for thrombocytopenia. Missed doses were also attributed to neurotoxicity in four patients (grade 2 to 3 sensory neuropathy), gastrointestinal toxicity in one patient who had bulky intra-abdominal disease that was shrinking on treatment, rash in two patients, and asthenia in three patients. Dose reductions from 1.5 to 1.3 mg/m^2 were noted in 14 patients (54%), largely as the result of thrombocytopenia before the protocol revision. Five patients (19%) had additional dose reductions from 1.3 to 1.1 mg/m^2. Twelve of the 25 patients (ie, 46%) tolerated the 1.5 mg/m^2 dose without significant toxicity or need for dose reduction.

Toxicity

A summary of the toxicity observed during this study is presented in Table 2. Other than thrombocytopenia, there were no other dose-limiting hematologic toxicities. Of note, grade 3 lymphopenia was seen in 14 patients (60%), suggesting intrinsic sensitivity of the lymphoid lineage to the effects of proteasome inhibition. This was not associated with an increase in opportunistic infections, although two patients developed an outbreak of shingles on study. Seven patients developed grade 3 thrombocytopenia. In general, all cytopenias were short lived, and resolved to baseline during the week off therapy. Electrolyte abnormalities including hyponatremia, which was a dose-limiting toxicity in the original phase I study, were also commonly seen among these patients. Three patients experienced hyponatremia (grade 3 or greater), two patients experienced hypokalemia (grade 3 toxicity), and one patient experienced hyperkalemia (grade 3 toxicity). In addition, several patients experienced an unusual rash, which after biopsy revealed a small-vessel necrotizing vasculitis. The rash typically appeared during cycles 3 and 4, approximately during the third or fourth doses of those cycles. The rash resolved during the week of rest from treatment (week 3), and met National Cancer Institute common toxicity criteria for a grade 1 vasculitis. In all cases, the rash was not associated with any adverse sequelae, nor could we document an associated presence of perinuclear antineutrophil cytoplasmic antibody or cytoplasmic antineutrophil cytoplasmic antibody.

Overall, two patients experienced grade 3 sensory neuropathy; one of these patients progressed into a grade 3 sensorimotor neuropathy. A thorough work-up of her condition at the time, including multiple magnetic resonance imaging studies and lumbar punctures to rule out leptomeningeal disease, and an electromyelogram (EMG), were all consistent with a likely pre-existing underlying neurologic disorder. The EMG analysis revealed complex repetitive discharges in both the paraspinal muscles and tongue. The electrophysiologic studies were interpreted as being most consistent with severe motor and sensory axonal polyneuropathy, although this possibly was not attributable to bortezomib. Electrophysiologic evidence for a widespread denervating process affecting motor nerves at all spinal levels and the tongue was also noted. A sural nerve biopsy confirmed marked axonal loss and axonal degeneration.

Table 2. Major Hematologic and Nonhematologic Toxicities for Patients Receiving Bortezomib

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
AST	14	1	0	0
ALT	6	3	1	0
Alkaline phosphatase	8	1	1	0
Bilirubin	4	3	0	0
Creatinine	5	1	0	0
Hemoglobin	17	5	1	0
Hyperglycemia	20	0	0	0
Hyperkalemia	3	0	1	0
Hypernatremia	7	0	0	0
Hypoalbuminemia	10	2	0	0
Hypocalcemia	6	5	0	0
Hypoglycemia	6	0	0	0
Hypokalemia	3	0	2	0
Hypomagnesemia	3	0	0	0
Hyponatremia	6	0	2	1
Hypophosphatemia	0	3	0	0
Infection without neutropenia	0	0	2	0
Leukocytes	14	9	1	0
Lymphopenia	0	0	14	0
Nausea	11	1	1	0
Neuropathic pain	13	2	0	0
Neuropathy, sensory	15	2	2	0
Neutrophils	10	7	1	0
PT	3	2	2	0
PTT	6	1	0	0
Thrombocytopenia	21	10	7	0
Vasculitis	2	1	0	0
Anorexia	2	1	1	0
Constipation	8	2	1	0
Diarrhea	11	1	0	0
Fatigue	14	3	1	0

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time.

Response

Table 3 lists the response data from the 26 registered patients; 24 of those patients were assessable for response. Figure 1 is a histogram of the response as a function of the disease subtype and overall best and worse response. Seven of the nine assessable patients with follicular lymphoma achieved objective remissions of their disease, with one CR and one CRu. In all patients, the remissions were confirmed at 1 month, and in all patients, the bulkiness of the disease did not seem to influence response. One patient in PR is still in active follow-up more than 20 months from the end of treatment with bortezomib. She achieved only a 7-month duration of remission from her prior therapy, which was rituximab. In all, 77% of the patients with follicular

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