A Phase I Study of Samarium Lexidronam/Bortezomib Combination Therapy for the Treatment of Relapsed or Refractory Multiple Myeloma

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Abstract

Purpose: This open-label, phase I dose-escalation study assessed the safety, tolerability, and initial efficacy of Samariam 153 (^{153}Sm)-lexidronam/bortezomib combination therapy for patients with relapsed/refractory multiple myeloma.

Experimental Design: Patients were enrolled in six cohorts and given bortezomib (1.0 or 1.3 mg/m^2) on days 1, 4, 8, and 11 and ^{153}Sm-lexidronam (0.25, 0.5, or 1.0 mCi/kg) on day 3 of a 56-day cycle (maximum of four cycles). The primary endpoints were safety and tolerability of the ^{153}Sm-lexidronam/bortezomib regimen.

Results: Twenty-four patients were enrolled. Median values for age, time since diagnosis, and number of prior treatments were 63 years, 29 months, and three regimens, respectively. The most common toxicities were hematologic; during the first cycle, median neutrophil and platelet nadirs were 1,000/mm^3 and 98,500/mm^3, respectively, and observed generally 3 to 4 weeks post-treatment. The incidences of grade 4 neutropenia and thrombocytopenia were 12.5% and 8.3%, respectively, during treatment cycle 1. Dose-limiting toxicity, reached in cohort 6 as a result of hematologic toxicity, defined the maximum tolerated dose as 0.5 mCi/kg ^{153}Sm-lexidronam in combination with 1.3 mg/m^2 bortezomib. The maximum tolerated dose for ^{153}Sm-lexidronam in combination with the 1.0 mg/m^2 bortezomib was not reached. No nonhematologic dose-limiting toxicities were observed; both the incidence and the severity of peripheral neuropathy were low. Responses occurred in 5 (21%) patients, including 3 (12.5%) complete and 2 (8.3%) minimal responses.

Conclusions: Bortezomib combined with ^{153}Sm-lexidronam appears to be a well-tolerated regimen, which showed clinical activity in this phase I trial for patients with relapsed or refractory multiple myeloma.

Multiple myeloma often responds to treatment with alkylating agents, glucocorticosteroids, and anthracyclines. Recent studies have also shown the clinical activity of the proteasome inhibitor bortezomib, thalidomide, lenalidomide, and arsenic trioxide (1, 2). These new agents and their combinations have shown increased response rates and have added more options for multiple myeloma patients whose disease has become resistant to conventional therapy. However, the disease remains incurable.

Because the disease is based in the bone marrow, patients with multiple myeloma often suffer from skeletal-related complications stemming from increased osteoclastic bone resorption that is not accompanied by a compensatory increase in bone formation (3). Consequently, clinical manifestations such as diffuse osteopenia, focal lytic lesions, pathologic fractures, hypercalcemia, and bone pain frequently occur in patients with multiple myeloma (3) and often lead to the requirement for radiation therapy, surgery, and analgesics (3, 4). Intravenous bisphosphonates are often administered monthly to patients with multiple myeloma to reduce the development of skeletal complications, especially new fractures and the requirement for radiation therapy.[6] However, these agents have also been associated with osteonecrosis of the jaw and occasional cases of renal failure (3, 5, 6). In addition, although bisphosphonates reduce skeletal complications, patients still commonly develop these problems. Therefore, new therapeutic options are needed not only to treat multiple myeloma but also to reduce the skeletal complications and associated bone pain that commonly occur in these patients.

Bortezomib is a novel first-in-class proteasome inhibitor indicated for the treatment of patients with multiple myeloma or mantle cell lymphoma who have received at least one prior therapy (7). The clinical efficacy and safety of single-agent

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Translational Relevance

Despite the development of new agents targeting multiple myeloma that have increased response rates and improved survival, this B-cell malignancy remains incurable. Because multiple myeloma is bone marrow-based, patients risk skeletal complications that can profoundly affect their quality of life even in those responsive to anti-multiple myeloma treatments. Therefore, new therapies for both multiple myeloma and its associated skeletal complications are needed.

Bortezomib as a single agent has clinical activity in multiple myeloma; *in vitro*, it has also been shown to enhance the antitumor effects of radiotherapy. ^{153}Sm-lexidronam is indicated for pain relief in patients with metastatic bone lesions and has been included as a potential anti-multiple myeloma agent in preparative chemotherapeutic regimens for stem cell transplants. In preclinical studies, the ^{153}Sm-lexidronam/bortezomib combination has shown significant, synergistic anti-multiple myeloma activity both *in vitro* and in murine models *in vivo*.

Our phase I clinical study suggests that this combination may be of particular value as a novel therapeutic option for the management of relapsed/refractory multiple myeloma. This novel therapeutic approach appears to be safe and well tolerated and may overcome resistance to standard chemotherapy, bortezomib, and thalidomide. We have established the maximum tolerated dose, providing the basis for further trials of this combination in relapsed or refractory multiple myeloma.

bortezomib in the treatment of relapsed or refractory multiple myeloma were shown in phase III Assessment of Proteasome Inhibition for Extending Remissions study (8, 9). Compared with high-dose dexamethasone, bortezomib produced responses in more patients (18% versus 38%; $P < 0.001$), extended the median time to progression (3.49 versus 6.22 months; $P < 0.001$), and increased the 1-year survival rate (66% versus 80%; $P = 0.003$; ref. 8). The time to first skeletal event, however, was not different between the two treatment groups, indicating that bortezomib did not significantly affect skeletal complications (8). Peripheral neuropathy, occurring in 36% of patients (8% grade 3/4), was the most clinically significant adverse event associated with this drug (8).

Preclinical studies have shown that bortezomib can sensitize chemoresistant myeloma cells to the cytotoxic effects of chemotherapy (10–12). Chemoresistant cell lines exposed to noncytotoxic levels of bortezomib in combination with melphalan, doxorubicin, or mitoxantrone show significantly reduced cell viability at concentrations of chemotherapy 10^5- to 10^6-fold lower than those required to induce cell death in the absence of bortezomib (10). These studies indicate that bortezomib can act as a chemosensitizing agent in the preclinical setting. Results from clinical studies support the relevance of the chemosensitizing effect of this agent for patients with relapsed or refractory multiple myeloma (13–15).

Recent studies also show the radiosensitizing effects of bortezomib in a variety of preclinical models (16). However, clinical studies showing this effect have not been published previously. ^{153}Sm-lexidronam is a radiopharmaceutical agent consisting of radioactive ^{153}Sm and a bone-seeking tetraphosphonate chelator, ethylenediaminetetramethylene-phosphonic acid. This agent is indicated for the relief of pain for patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan (17). This radiopharmaceutical has also been evaluated as a potential anti-myeloma drug. Specifically, high doses of ^{153}Sm-lexidronam have been used as part of preparative regimens for stem cell transplantation for multiple myeloma patients with promising clinical results (18, 19). The addition of ^{153}Sm-lexidronam to standard preparative regimens of melphalan or cyclophosphamide resulted in high overall response rates (86-94%) with no reported dose-limiting toxicities (DLT; refs. 18, 19). In preclinical studies, the combination of ^{153}Sm-lexidronam and bortezomib showed synergistic anti-myeloma activity (16). Human multiple myeloma cell lines exposed to this combination *in vitro* had significantly reduced cell viability, and mice injected with murine multiple myeloma cells and subsequently treated with both drugs had significantly prolonged median survival times, reduced paraprotein levels, and improved bone mineral density compared with mice treated with either agent alone, without affecting blood counts.

Because of these results and the fact that ^{153}Sm-lexidronam delivers high doses of radiation that concentrate in tumor-infiltrated bone and bone marrow (20), and because bortezomib has shown radiosensitizing effects in the laboratory, we chose to conduct a phase I study to assess the safety, tolerability, and initial efficacy of ^{153}Sm-lexidronam and bortezomib combination therapy for patients with relapsed or refractory multiple myeloma.

Materials and Methods

Study design. This trial was a phase I, open-label dose-escalation study designed to evaluate the safety, tolerability, and efficacy of bortezomib in combination with ^{153}Sm-lexidronam for patients with relapsed or refractory multiple myeloma. Institutional review board approval and individual informed written consent from the patients were obtained before patients were enrolled in the study. Patients with relapsed or refractory multiple myeloma were alternately assigned to one of six cohorts in the following treatment arms: bortezomib at 1.0 mg/m^2 and three escalating doses of ^{153}Sm-lexidronam (0.25, 0.5, and 1.0 mCi/kg) or bortezomib at 1.3 mg/m^2 and the same three escalating doses of ^{153}Sm-lexidronam (0.25, 0.5, and 1.0 mCi/kg; Table 1). At least 3 patients were planned to be enrolled at each dose level. The ^{153}Sm-lexidronam dose was escalated if patients at the previous dose levels tolerated the treatment without DLTs. Each treatment cycle lasted 8 weeks and consisted of one intravenous injection of ^{153}Sm-lexidronam on day 3, and 4 intravenous injections of bortezomib infused over 3 to 5 s on days 1, 4, 8, and 11, followed by a 45-day rest period. Patients were allowed to receive additional cycles of treatment (to a maximum of four) if they exhibited either a disease response or stable disease in their prior treatment cycle and continued to fulfill the original eligibility criteria. Safety data sufficient to preclude DLTs were obtained at each dose level before patients were enrolled in the next higher dose level.

Patient selection. Men and women ages ≥18 years with relapsed or refractory multiple myeloma who showed measurable disease (defined as a monoclonal immunoglobulin spike on serum electrophoresis of ≥1 g/dL and/or urine monoclonal immunoglobulin spike of ≥200 mg/24 h or evidence of lytic bone disease) were enrolled in this

study. Before enrollment, patients had to have relapsed after a response to, or disease stabilization resulting from, standard or high-dose chemotherapy or be refractory to their most recent chemotherapy treatment. Patients had to have a life expectancy of >3 months, Karnofsky performance status ≥60, baseline platelet count ≥75,000/mm^3, and absolute neutrophil count (ANC) ≥1,500/mm^3.

Patients were excluded from the study if they had plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome; plasma cell leukemia; major surgery within 4 weeks of the screening visit; active infection (including HIV and hepatitis B or C); New York Hospital Association class III or IV heart failure; severe hypercalcemia (serum calcium ≥14 mg/dL or 3.5 mmol/L); chemotherapy within 3 weeks or nitrosoureas within 6 weeks of study enrollment; corticosteroids (>10 mg/d prednisone or equivalent) within 3 weeks of study enrollment; immunotherapy, antibody therapy, or radiation therapy within 4 weeks of study enrollment; grade >1 neuropathy at baseline; or extramedullary myeloma. Pregnant and nursing women were also excluded.

Pretreatment assessments. A screening visit was conducted within 14 days of day 1 of cycle 1, during which a medical history and complete physical and neurologic examinations were obtained. Vital signs, Karnofsky performance status, height, and weight were measured, and a 12-lead electrocardiogram and posteroanterior and lateral chest X-rays were done. Screening disease assessments included serum β_2-microglobulin, C-reactive protein, serum and urine electrophoresis, quantitative immunoglobulin measurement, urine and serum immunofixation, 24-h total protein, skeletal survey, and bone marrow aspirate and biopsy. Clinical screening laboratory tests were also done at this visit, including complete blood cell count, platelet count, clinical chemistry, electrolytes, amylase, urinalysis, and serum pregnancy tests for women of childbearing potential.

Safety assessments. Adverse events were monitored before each study drug dose was administered. In addition, complete blood cell count, platelet counts, and review of concomitant medications and supportive therapies were done on days 1, 4, 8, 11, 15, 22, 29, 36, 43, and 50 of each cycle. Interval history, neurotoxicity interview, and symptom-directed physical examination were done on days 4, 8, and 11, and complete physical and neurologic examinations were done on days 1, 29, and 50 of each cycle. Clinical chemistry analysis and urinalysis were done on days 1, 29, and 50 of cycle 1 and on days 29 and 50 of subsequent cycles.

Toxicities were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. A DLT was defined as any of the following events occurring during the first cycle of treatment: grade 4 hematologic toxicity (regardless of duration), grade 3 febrile neutropenia, study drug-related grade 3 or 4 non-hematologic toxicity, or study drug-related death. Additionally, any study drug-related treatment delay or interruption of >4 weeks or missing three of four bortezomib doses in a single treatment cycle because of toxicity was also considered a DLT. If a DLT was not observed in 3 patients at a dose level during the first cycle, patients were enrolled to the next higher dose level. However, if 1 patient at any dose level experienced a DLT during the first cycle, a maximum total of 6 patients were recruited to that dose level; if a DLT was seen in 2 patients, no additional patients were recruited to that level. The maximum tolerated dose was defined as the highest dose level at which <33% of patients experienced a DLT.

Table 1. Dose-escalation schema

Cohort number (*n*)	^{153}Sm-lexidronam (mCi/kg)	Bortezomib (mg/m^2)
1 (3)	0.25	1.0
2 (3)	0.5	1.0
3 (6)	1.0	1.0
4 (3)	0.25	1.3
5 (3)	0.5	1.3
6 (6)	1.0	1.3

Efficacy assessments and response criteria. Patient responses to treatment were monitored on days 29 and 50 of each cycle as determined through assessment of serum β_2-microglobulin, C-reactive protein, serum protein electrophoresis, immunofixation, quantitative immunoglobulins, and 24-h urine protein and electrophoresis. Responses to study treatment were evaluated according to European Group for Blood and Marrow Transplantation criteria (21). All responses had to be confirmed with repeat laboratory assessment at least 3 weeks from the prior tests. Responses not meeting the criteria for minimal response or progressive disease were classified as no change.

Data analysis. The primary endpoint of this study was the safety and tolerability of ^{153}Sm-lexidronam/bortezomib combination therapy, as reflected in the maximum tolerated dose and DLT, for patients with relapsed or refractory multiple myeloma. Descriptive statistics were used for characterization of these safety variables as well as disease characteristics and baseline patient characteristics. Secondary endpoints included the overall proportion of patients responding to therapy (complete response + partial response + minimal response).

Results

Patient disposition. Twenty-four patients were enrolled in the study between December 1, 2005 and January 2, 2007. The patients were predominantly male (71%) and Caucasian (92%), with a median age of 63 years (range, 44-78). The median time from diagnosis of multiple myeloma to study entry was 29 months (range, 7-114 months). All patients had received prior therapy for their disease, with most (62%) having received at least three prior regimens (range, 1-8). Thirteen (54%) patients had received prior treatment with bortezomib and 12 (50%) received prior treatment with melphalan; 10 (42%) had previously received both agents. Among patients previously treated with bortezomib-containing regimens, all had progressed following those regimens, and the median interval between the time of that progression and the initiation of the study treatment was 7 months. Twelve (50%) patients received prior treatment with thalidomide and 6 (25%) received prior treatment with lenalidomide; 4 (17%) had previously received both agents. No patient had previously received ^{153}Sm-lexidronam. Patient demographics and baseline characteristics are further described in Table 2.

Ten patients received at least two cycles of treatment; 7 patients received at least three cycles and 5 patients completed all four cycles. The remaining patients (n = 14), who received only one cycle of therapy, were withdrawn (per protocol) because they failed to attain either a disease response or stable disease in their initial treatment cycle.

Safety and tolerability. The only clinically significant toxicity associated with coadministration of ^{153}Sm-lexidronam and bortezomib was a generally mild, transient myelosuppression. Among all enrolled patients, five incidents of DLT occurred in 4 patients in cycle 1. In cohort 3 (1.0 mCi/kg ^{153}Sm-lexidronam and 1.0 mg/m^2 bortezomib), 1 patient had an ANC nadir of 300/mm^3 at day 15 and a platelet nadir of 24,000/mm^3 at day 27, prompting expansion of the cohort. No further DLTs were seen in this cohort, and none of the other 5 patients in the cohort had neutrophil or platelet toxicities more severe than

Table 2. Patient demographics and baseline characteristics (n = 24)

Characteristics	
Median (range) age, y	63 (44-78)
Gender, *n* (%)	
Female	7 (29)
Male	17 (71)
Baseline labs; median (range)	
Albumin (g/dL)	3.3 (2.2-4.5)
Creatinine (mg/dL)	1.0 (0.7-2.4)
β_2-Microglobulin (ng/L)	2.56 (0.06-8.28)
M protein (mg/24 h)	1.82 (0-6.85)
LDH (units/L)	130 (83-543)
Hemoglobin (g/dL)	11.9 (7.9-15.7)
Median (range) no. prior therapies	3 (1-8)
Prior therapies, *n* (%)	
Bortezomib	13 (54)
Melphalan	12 (50)
Thalidomide	12 (50)
Lenalidomide	6 (25)
Arsenic trioxide	4 (17)
Median duration of disease (range), mo	29 (7-114)

grade 2. In cohort 6 (1.0 mCi/kg ^{153}Sm and 1.3 mg/m^2 bortezomib), there were two occurrences of grade 4 neutropenia (ANC nadirs of 400/mm^3 and 470/mm^3 on days 50 and 43, respectively), and one occurrence of grade 4 thrombocytopenia (platelet nadir of 15,000/mm^3 on day 15), establishing dose-limiting hematologic toxicity at this level. Thus, when administered in combination with 1.3 mg/m^2 bortezomib, the maximum tolerated dose of ^{153}Sm-lexidronam was found to be 0.5 mCi/kg. When administered in combination with 1.0 mg/m^2 bortezomib, the maximum tolerated dose of ^{153}Sm-lexidronam was not reached with the highest administered dose level of 1.0 mCi/kg.

Nadirs of ANC and platelet counts as well as the frequency of grade 3 and 4 toxicities for all cohorts during the first treatment cycle are presented in Table 3. Nadir values were similar across all cohorts and generally occurred between 15 and 29 days after initial treatment. Median nadir values for ANC and platelets for all patients in cycle 1 were 1,000/mm^3 and 98,500/mm^3, respectively (Table 4). Because only 20% of patients completed all treatment cycles, it is not possible to systematically compare cohorts in cycles 2 to 4. However, among all patients receiving multiple cycles, there was very little change in median nadir values for ANC and platelets across the first three cycles. Median levels were slightly lower following the fourth cycle; however, there were no instances of dose-limiting hematologic toxicity in cycle 4. The incidences of grade 4 neutropenia and thrombocytopenia were 12.5% and 8.3%, respectively, following cycle 1, and 8.7% and 13.0%, respectively, following all cycles administered. For patients experiencing grade 4 neutropenia (following any cycle), the median time to recovery to an ANC >1,000/mm^3 was 15 days; for patients experiencing grade 4 thrombocytopenia, the median time to a platelet count >50,000/mm^3 was 17 days.

The majority of nonhematologic adverse events were mild to moderate in severity, and no nonhematologic DLTs were observed during the study. There were no treatment-related fatalities, and no patient required a delay of cycle or interruption of bortezomib for >4 weeks. A single grade 4 nonhematologic adverse event was observed: a case of appendicitis occurred on day 40 of the third treatment cycle in a patient whose neutrophil count was within normal limits at the time of the event. The patient was treated surgically and recovered without complications.

Only 3 (12.5%) patients either developed or had a worsening of peripheral neuropathy following treatment: 2 patients developed grade 1 peripheral neuropathy each during their third treatment cycle and the third patient, who had grade 1 peripheral neuropathy at baseline, worsened to grade 2 during treatment cycle 3 and to grade 3 during treatment cycle 4.

Efficacy. In this phase I trial, the overall response rate among all cohorts was 21%, including 12.5% complete response and 8.3% minimal response. There was no clear dose dependence of either rates of overall response or complete response. Two of the patients who achieved complete response received a bortezomib dose of 1.0 mg/m^2, and one complete response was achieved at each of the three dose levels of ^{153}Sm-lexidronam. Both patients who achieved minimal response received a bortezomib dose of 1.3 mg/m^2, one of whom received a ^{153}Sm-lexidronam dose of 0.5 mCi/kg and the other 1.0 mCi/kg. However, interpretation of these findings is limited by the small number of patients evaluated in each cohort in this phase I trial. The overall response rate for patients previously treated with a bortezomib-containing regimen was 15% compared with 27% in patients whose prior treatments did not include bortezomib. Notably, the 2 patients who achieved minimal response initiated treatment on this trial

Table 3. ANC and platelet nadirs: cycle 1

Cohort	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
^{153}Sm (mCi/kg)	0.25	0.5	1.0	0.25	0.5	1.0
Bortezomib (mg/m^2)	1.0	1.0	1.0	1.3	1.3	1.3
(no. patients)	(*n* = 3)	(*n* = 3)	(*n* = 6)	(*n* = 3)	(*n* = 3)	(*n* = 6)
ANC nadir ($\times 10^3$/mm^3)						
Median (range)	1.0 (0.8-1.9)	1.1 (0.9-3.4)	1.5 (0.3-2.2)	0.84 (0.82-0.85)	1.2 (1.2-2.7)	0.7 (0.4-1.9)
Median time to nadir, d	15	15	29	15	15	32
No. with grade 3/4 neutropenia	0/0	1/0	0/1	3/0	0/0	3/2
Platelet count nadir ($\times 10^3$/mm^3)						
Median (range)	96 (84-162)	101 (78-129)	86 (24-174)	88 (74-172)	144 (119-157)	74 (15-153)
Median time to nadir, d	36	15	32	15	29	15
No. with grade 3/4 thrombocytopenia	0/0	0/0	0/1	0/0	0/0	2/1

Table 4. Median (range) ANC and platelet nadirs: all cycles

	Cycle 1 (*n* = 24)	Cycle 2 (*n* = 10)	Cycle 3 (*n* = 7)	Cycle 4 (*n* = 5)
ANC nadir, $\times 10^3/mm^3$ (range)	1.0 (0.3-3.4)	1.1 (0.4-2.9)	1.1 (0.7-2.1)	0.8 (0.7-1.9)
No. with grade 3/4 neutropenia	7/3	2/1	2/0	2/0
Platelet count nadir, $\times 10^3/mm^3$ (range)	98.5 (15-193)	92 (13-151)	97 (15-130)	66 (36-121)
No. with grade 3/4 thrombocytopenia	2/2	$^1/_2$	0/2	1/0

within 12 and 28 days of having received and progressed from a more frequent dosing regimen (four doses every 4 weeks) of bortezomib with oral melphalan. Table 5 presents the prior treatment regimens and best prior response for patients achieving response in this trial. Disease remained stable following three 8-week treatment cycles in 2 patients and following four cycles in 1 additional patient. No patient experienced a skeletal-related event (pathologic fractures, spinal cord compression/collapse, surgery, or radiation to bone) while on study, but patients were also treated with monthly intravenous bisphosphonate therapy.

Discussion

Although multiple myeloma is initially sensitive to chemotherapy (22) and radiation therapy (23), it remains incurable (2, 11). Patients eventually relapse as their tumor cells develop resistance (22), and the ability to overcome resistance to anti-multiple myeloma treatments is critically important in improving outcomes for patients with multiple myeloma (24).

The ability of the proteasome inhibitor bortezomib to sensitize chemoresistant myeloma cells (10) and its synergistic activity with ionizing radiation (25) and ^{153}Sm-lexidronam radionuclide therapy (16) render it a promising agent for combination approaches for patients with relapsed or refractory multiple myeloma. The radiosensitizing effects of bortezomib may result from the inhibition of nuclear factor-κB survival signaling, cell cycle arrest at the radiosensitive G_2-M phase, and enhancement of apoptosis by inducing the Fas death receptor (16).

^{153}Sm-lexidronam avidly targets bone, with skeletal uptake ranging between 55% and 75% (20). Emission of β-particles with a range of ~3 mm allows targeting of effective doses of radiation while essentially sparing nonhematopoietic tissue (16, 26). Although ^{153}Sm-lexidronam has been viewed as a palliative therapy for metastatic bone disease, emerging evidence suggests that this radiopharmaceutical also has anti-myeloma activity. Findings from a phase I study of ^{153}Sm-lexidronam and zoledronic acid for patients with refractory multiple myeloma suggested that the combination was synergistic: in addition to providing quality-of-life benefits, in 4 of 8 patients receiving the combination, the serum M-component decreased >25% (27).

This phase I study has shown that ^{153}Sm-lexidronam/bortezomib has antitumor activity for patients with relapsed or refractory multiple myeloma. Bortezomib is typically administered on days 1, 4, 8, and 11 followed by a 10-day rest period (7); this study incorporated a prolonged rest period of 45 days to allow recovery from any deleterious effects on marrow function from ^{153}Sm-lexidronam. Despite this modified dosing schedule for bortezomib, responses were observed in this study at a rate of 21%, including 12.5% complete response and 8.3% minimal response. By comparison, the overall response rate for bortezomib in the Assessment of Proteasome Inhibition for Extending Remissions study was 46%, with 6% complete response, 32%

Table 5. Best prior response and time to progression for current responders

Cohort no.	Patient no.	Prior treatment regimen(s)	Best prior response	^{153}Sm-lexidronam (mCi/kg)	Bortezomib (mg/m^2)	Response to ^{153}Sm-lexidronam/bortezomib	Time to progression (mo)
2	09	Doxorubicin/vincristine/dexamethasone	CR	0.5	1.0	CR	4.1
3	18	Melphalan/prednisone Thalidomide	SD	1.0	1.0	CR	7.2
4	06	Doxorubicin/vincristine/dexamethasone	SD	1.0	1.3	CR	7.1
5	12	Thalidomide Thalidomide/methylprednisolone Melphalan/bortezomib	PR	0.25	1.3	MR	8.3
6	20	Melphalan/bortezomib	MR	0.5	1.3	MR	6.4

Abbreviations: CR, complete response; PR, partial response; MR, minimal response; SD, stable disease.

partial response, and 8% minimal response (8). However, many patients enrolled in our trial had previously received treatment with bortezomib. Notably, 2 patients who responded to this less frequently dosed bortezomib with ^{153}Sm-lexidronam received study treatment within 1 month of progressing from a combination of oral melphalan and bortezomib on a more frequent dosing (four doses every 4 weeks) schedule. These results suggest that the ^{153}Sm-lexidronam/bortezomib combination can achieve responses even among patients resistant to bortezomib/chemotherapy combination therapies.

Although the patients enrolled on this trial were heavily pretreated, the combination of bortezomib and ^{153}Sm-lexidronam was generally well tolerated, with the majority of adverse events mild to moderate in severity. Consistent with the toxicity profiles of ^{153}Sm-lexidronam and bortezomib, the most common toxicities associated with the combination therapy were hematologic.

Thrombocytopenia is a frequent complication of chemotherapy that may necessitate dose reductions or schedule delays (28). In the randomized phase III clinical trial comparing bortezomib (1.3 mg/m^2) with high-dose dexamethasone for relapsed multiple myeloma, the incidences of grade 3 and 4 thrombocytopenia in the bortezomib arm were 26% and 4%, respectively, with 4% of patients experiencing clinically significant bleeding episodes (8).

Myelosuppression is a known side effect of bone-targeted radionuclides because they irradiate the bone marrow (29). The mechanism of ^{153}Sm-lexidronam-induced thrombocytopenia has not been fully elucidated; however, platelet function remains stable (30), although the aggregation response is slightly diminished due to the decreased number of circulating platelets at the platelet nadir (3-4 weeks). We did observe evidence of dose-related thrombocytopenia in this trial, which is an expected complication among patients receiving this combination. In our study, no significant dosing delays or bleeding episodes were observed. Platelet counts should be carefully monitored in patients receiving this regimen. Overall, our results, combined with those from previous studies showing the lack of cumulative toxicity (31) and the absence of late toxic effects or interference with bone marrow recovery, highlight the potential role of the combination of these two agents in the management of relapsed or refractory multiple myeloma.

Importantly, both the incidence (12.5%) and the severity of peripheral neuropathy were low in this study, in which patients received 1.0 or 1.3 mg/m^2 bortezomib twice weekly for 2 consecutive weeks of an 8-week cycle rather than the typical 3-week cycle. All three cases occurred following a third cycle of treatment. By comparison, peripheral neuropathy was reported in 36% of patients (grade 3 in 8%) in the Assessment of Proteasome Inhibition for Extending Remissions study, in which patients received bortezomib more frequently, at a dose of 1.3 mg/m^2 twice weekly for 2 weeks for eight 3-week cycles and then once weekly for 4 weeks for three 5-week cycles (8). The longer rest period (45 days) between bortezomib dosing in this study and/or the use of bortezomib at lower doses in combination with other agents may reduce the occurrence and severity of peripheral neuropathy.

Finally, several patients experienced reductions in skeletal-related pain and improvements in quality of life, although this was not formally assessed in this phase I trial. This finding is consistent with those previously reported for ^{153}Sm-lexidronam for patients with bone pain from bone metastases from several solid tumors including prostate and breast cancers and osteosarcoma (31–33). Reduction in pain and improvement in quality of life are important clinical benefits for patients with relapsed or refractory multiple myeloma, and future studies should include formal evaluation of these variables.

Conclusion

The findings from this phase I study have established the maximum tolerated dose for ^{153}Sm-lexidronam (0.5 mCi/kg) in combination with 1.3 mg/m^2 bortezomib and the lack of DLT for 1.0 mCi/kg ^{153}Sm-lexidronam (the Food and Drug Administration-approved dose) in combination with 1.0 mg/m^2 bortezomib. They also support the efficacy of ^{153}Sm-lexidronam/bortezomib for patients with relapsed or refractory multiple myeloma, with an overall response rate of 21% and a complete response rate of 12.5%. These responses show the efficacy of this regimen in heavily pretreated patients, including some who had recently failed bortezomib/melphalan combination treatment. ^{153}Sm-lexidronam/bortezomib combination therapy was well tolerated, with predictable and manageable primarily hematologic side effects consistent with those associated with ^{153}Sm-lexidronam and bortezomib monotherapy. These results suggest potential clinical benefits and warrant further evaluation of this regimen for patients with relapsed or refractory multiple myeloma. In addition, this study should provide impetus for evaluating the radiosensitizing effects of bortezomib in other clinical settings.

Disclosure of Potential Conflicts of Interest

J.R. Berenson is a consultant and member of the speakers' bureau for Millennium Pharmaceuticals and has received grant/research support from Millennium Pharmaceuticals and Cytogen. R.A. Swift is a member of the speakers' bureaus of Millennium Pharmaceuticals and Novartis Pharmaceuticals. The other authors disclose no potential conflicts.

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