Phase I Study of Concurrent Weekly Docetaxel and Repeated Samarium-153 Lexidronam in Patients With Castration-Resistant Metastatic Prostate Cancer

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ABSTRACT

Purpose

Samarium-153 (¹⁵³Sm) lexidronam is a bone-targeting radiopharmaceutical with a short physical half-life and a favorable toxicity profile. We evaluated the safety and feasibility of a concurrent combination of weekly docetaxel with repeated ¹⁵³Sm-lexidronam in patients with castration-resistant prostate cancer (CRPC).

Patients and Methods

A conventional 3 + 3 dose-escalation design was used for this study. Patients were treated in three cohorts comprising two cycles of weekly docetaxel at 25, 30, and 35 mg/m², respectively, on days 1, 8, and 15 of a 28-day cycle in combination with ¹⁵³Sm (1 mCi/kg) on day 1. Unacceptable hematologic toxicity (UHT) was defined as more than 7 days delay in therapy for inadequate counts: an absolute neutrophil count (ANC) more than 1,000/μL and platelets more than 70,000/μL were required at days 8 and 15 and ANC more than 1,500/μL and platelets more than 100,000/μL were required at cycle 2, day 1. If counts had not recovered by day 56 of either combination cycle, UHT was declared.

Results

Eighteen patients were treated in three cohorts. Two patients in separate cohorts experienced UHT; the maximum-tolerated dose for this regimen was not reached. The median interval between ¹⁵³Sm doses was 35 days (range, 27 to 57 days). The only significant toxicity was mild, transient myelosuppression. Five patients (28%) experienced grade 3 hematologic toxicity. There were no grade ≥ 4 hematologic or nonhematologic toxicities.

Conclusion

Two dosing cycles consisting of weekly docetaxel and monthly ¹⁵³Sm-lexidronam were well tolerated and feasible in this CRPC population.

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INTRODUCTION

Prostate cancer spreads to the bone in a preferential manner, with bone the only site of clinical metastasis in a majority of patients presenting with metastatic prostate carcinoma.¹ Progression to the bone can cause substantial morbidity, including pain, impaired mobility, pathologic fracture, spinal cord or nerve root compression, and marrow infiltration. Skeletal complications contribute to a significant impairment in health-related quality of life.² In patients with advanced prostate cancer, hormonal or cytotoxic chemotherapy can palliate symptoms, delay progression, and prolong survival. There is evidence that soluble factors produced in the bone marrow may contribute to tumor cell survival and treatment resistance.³⁻⁵ Consequently,

bone-targeted therapies that directly or indirectly affect bone metastasis may improve current treatments of prostate cancer.⁶

Two bone-seeking radiopharmaceuticals, strontium-89 (⁸⁹Sr) chloride and samarium-153 (¹⁵³Sm) lexidronam, are currently approved by the United States Food and Drug Administration for the treatment of painful bone metastases. Bone-seeking radiopharmaceuticals target bone metastases by preferential deposition at sites of increased osteoblastic activity and bone matrix synthesis. Their unique physical properties allow them to irradiate multiple sites of skeletal metastases simultaneously. Therefore, these agents are ideally suited for the treatment of patients with advanced prostate cancer who develop multifocal osteoblastic metastases, particularly those for whom bone is the predominant or

sole site of metastasis. Another potential advantage of radiopharmaceuticals is that they can be used repeatedly for palliation of bone pain. Radiopharmaceuticals may also have a role beyond the palliation of pain, as they have been shown to limit or delay the development of new metastatic sites in bone.⁷

Early clinical data suggest that anthracyclines in combination with bone-seeking radiopharmaceuticals may prolong survival relative to chemotherapy alone in selected patients with castration-resistant metastatic prostate cancer.⁸ In the postanthracycline era, docetaxel-based therapies have emerged as a treatment of choice for patients with castration-resistant prostate cancer (CRPC). Docetaxel-based therapies provide substantial clinical benefit, including enhanced quality of life and prolonged overall survival.^{9,10} On the basis of the demonstrated benefits of both ¹⁵³Sm-lexidronam and docetaxel, combination therapies that incorporate these agents are being actively explored in clinical trials.¹¹

There is concern that combining chemotherapy with repeated and intensive radiopharmaceuticals could be prohibitively toxic. ¹⁵³Sm-lexidronam has a shorter half-life than ⁸⁹Sr chloride (1.9 v 50.5 days, respectively), which may lessen the toxicity profile of ¹⁵³Sm-lexidronam when combined with chemotherapy. We reasoned that a weekly schedule of docetaxel combined with ¹⁵³Sm might be safer with regard to hematologic toxicity because we could easily titrate and afford to use smaller doses of chemotherapy. In addition, patients who had received prior 3-week docetaxel could still respond to weekly docetaxel because of an entirely different (eg, metronomic) mechanism of action. We anticipated that patients who were older, who had prior therapies, or who had a worse performance status might tolerate better and benefit more from less chemotherapy provided that the radiopharmaceutical also substantially contributed to the therapeutic efficacy of a combination regimen.

The principal objective of this study was to evaluate the safety and tolerability of a regimen consisting of ¹⁵³Sm-lexidronam combined with docetaxel in patients with metastatic CRPC. Two cycles of ¹⁵³Sm-lexidronam at the approved dose for palliation of painful bone metastases (1.0 mCi/kg)^{12,13} were administered concurrently with a weekly regimen of docetaxel (25 mg/m², 30 mg/m², or 35 mg/m²).^{14,15} Because the side effects of chemotherapy and radiopharmaceuticals could include bone marrow suppression, myelosuppression was monitored as a measure of the feasibility of this combination regimen. In addition, because the timing of myelosuppression and recovery after the combination regimen has the potential to impact administration of both scheduled chemotherapy and subsequent combination treatment, the definitions of dose-limiting toxicity took these factors into account.

PATIENTS AND METHODS

Study Design

This study was designed to evaluate the safety profile of weekly docetaxel when administered in combination with two cycles of a fixed dosage of ¹⁵³Sm-lexidronam in patients with CRPC. Patients were assigned to three treatment cohorts on the basis of increasing docetaxel dose. A conventional 3 + 3 dose-escalation design was used wherein a first occurrence of unacceptable hematologic toxicity (UHT) resulted in the expansion of the cohort from three to six patients. The maximum-tolerated dose was defined as the highest dose level at which six patients were treated with fewer than three instances of UHT.

Patients

Major eligibility criteria included histologically confirmed adenocarcinoma of the prostate, progressive CRPC as defined by increasing prostate-specific antigen (PSA) on two occasions at least 2 weeks apart, and evidence of three or more bone metastases on bone scan. Patients had to have a life expectancy of 12 weeks or longer and a Zubrod scale performance status of 3 or less. They should not have had more than two prior cytotoxic chemotherapy treatments or two prior external-beam radiation courses to the bone. Patients could have received one prior treatment with ¹⁵³Sm or ⁸⁹Sr, provided initiation into the study was at least 12 weeks from treatment with ¹⁵³Sm or 24 weeks from treatment with ⁸⁹Sr. Individuals previously treated with bisphosphonates, secondary hormonal agents, corticosteroids, angiogenesis inhibitors, gene therapy, or immunotherapy were allowed. Patients with predominant lymphatic or visceral metastases and whose tumors contained small-cell carcinoma were excluded. They could not have New York Heart Association Class III or IV cardiovascular disease or a history of other malignancies (other than nonmelanoma skin cancer), unless in complete remission or off therapy for at least 5 years. Patients with known circumferential or transcortical long bone fractures (unless surgically stabilized) or spinal cord compression were also excluded.

In particular, each patient was required to have a WBC count of at least 3,000/ μ L, a platelet count $\geq$ 100,000/ μ L, an absolute neutrophil count (ANC) of at least 1,500/ μ L, a bilirubin concentration less than or equal to the upper limit of normal, a serum ALT/AST value less than 1.5 $\times$ the upper limit of normal, and a serum creatinine concentration of $\leq$ 2.0 mg/dL. The institutional review board of the University of Texas M. D. Anderson Cancer Center approved the study design and each patient provided written informed consent before enrollment.

Patient Monitoring

After the initial screening, and to monitor hematologic effects of treatment, each docetaxel treatment cycle began with a baseline laboratory assessment of CBC counts and adverse events. On days when ¹⁵³Sm was administered, laboratory assessments included PSA, serum biochemistries, and patient status on the basis of the Zubrod performance scale. Time to progression or progression-free survival was defined as the time from start of treatment to appearance of new lesions (excluding flare phenomena), symptoms of progressive disease, or PSA progression of 25% more than baseline.

Treatment With Study Drug

Each dosing cycle lasted a minimum of 4 weeks. ¹⁵³Sm-lexidronam was administered (1.0 mCi/kg) intravenously on day 1 and day 28. On dosing days that called for administration of both ¹⁵³Sm-lexidronam and docetaxel, the administration of ¹⁵³Sm-lexidronam was given 6 to 30 hours before the administration of docetaxel to allow for renal clearance. Docetaxel (25 mg/m², 30 mg/m², or 35 mg/m²) was administered intravenously over 1 hour on days 1, 8, and 15 of each cycle. All patients were premedicated with oral corticosteroids before docetaxel administration to prevent an acute drug reaction.

After the administration of the combination treatment, scheduled doses of docetaxel were given if the ANC was at least 1,000/ μ L and if the platelet count was more than 70,000/ μ L; otherwise, treatment was withheld for 1 week and counts were rechecked. If count recovery took longer than 1 week or if a patient had a second treatment delay, the patient was declared to have UHT, and additional treatment with docetaxel was given at a reduced dosage at the discretion of the treating physician.

The second dose of ¹⁵³Sm was administered if the platelet count was greater than 100,000/ μ L and the ANC was greater than 1,500/ μ L. When counts were below this range, patients were checked every 2 weeks for up to an additional 8 weeks. When counts had recovered to the specified levels, patients were administered the second dose of ¹⁵³Sm. If the counts had not recovered after 8 weeks, the patient was declared to have UHT. Docetaxel treatments were discontinued after the two courses of combination therapy on this study. Use of continuous low-dose corticosteroids was not required for this study.

In addition to UHT that prevented scheduled treatment with docetaxel and/or a second cycle of combination treatment, dose-limiting toxicity was also considered to have occurred if more than two patients in any cohort

experienced a grade 3 or at least one patient had a grade 4 nonhematologic toxicity during either treatment cycle.

RESULTS

Demographics

A total of 18 patients were enrolled onto this open-label dose-escalation study, six in each of the three cohorts. The demographics and treatment history were generally similar among the three cohorts (Table 1). The majority of patients in all groups had more than 10 lesions visible on bone scan. Baseline PSA values ranged from 7 to 1,348 ng/mL, with a median of 61 ng/mL for all patients. Sixteen patients (89%) had received prior chemotherapy. The most commonly administered agents included doxorubicin (44%), docetaxel (28%), and cyclophosphamide (22%). Of the patients previously treated with chemotherapy, eight (50%) had received one prior treatment regimen and the other eight (50%) had received two. Eleven patients (61%) had also received prior radiation therapy, including six patients who had received external-beam therapy (three to the prostate and three to the bone), three who had received ¹⁵³Sm, and two who had received ⁸⁹Sr.

Seventeen patients (94%) completed one full combination treatment cycle, and 13 patients (72%) completed both. Three patients, all from the first cohort, did not complete two cycles of treatment because of disease progression; one of these patients received both cycles of therapy but did not complete follow-up before being removed from the study with rapidly progressive disease and died within a month of being taken off study. He had clinical evidence of disseminated intravascular coagulopathy with increasing PSA levels and worsening epidural disease. The second, who had grade 2 weakness of the left lower extremity (because of a large left iliac mass at baseline), completed

cycle 1 but was removed from the study because of progressive disease causing a mild T6 spinal cord compression. The third completed cycle 1 but was removed from the study as a result of progression of disease with a rapidly increasing PSA and worsening bone pain. All three of these patients were replaced. Two patients were removed from the study as a result of UHT: one patient in cohort 2 received two doses of docetaxel and at week 8 of combination cycle 1 had an ANC of 1,400/ μ L and another patient in cohort 3 had a platelet count of 62,000/ μ L at week 8 of combination cycle 1. As a result, both cohorts two and three were expanded to six patients with no additional occurrences of UHT.

Hematologic Safety

As in earlier studies, the only clinically significant toxicity associated with coadministration of ¹⁵³Sm-lexidronam and docetaxel was mild, transient myelosuppression. After the first ¹⁵³Sm infusion, nadir ANC and platelet counts averaged 2,280/ μ L (standard deviation [SD], $\pm$ 1,720/ μ L) and 133,000/ μ L (SD, $\pm$ 69,000/ μ L), respectively (Table 2). For all patients, nadirs were observed a median of 28 days after administration. For cycle 2, nadir levels for ANC and platelets averaged 2,040/ μ L (SD, $\pm$ 1,120/ μ L) and 161,000/ μ L (SD, $\pm$ 76,000/ μ L) and were observed a median of 15 days and 22 days, respectively, after infusion. The nadir levels and time to nadir were similar for all treatment cohorts (Table 2), demonstrating the three docetaxel doses resulted in similar levels of myelosuppression when administered concurrently with ¹⁵³Sm-lexidronam. In addition, prior radiopharmaceutical administration or the extent of prior chemotherapy did not seem to affect the nadir ANC or platelet count after either cycle of therapy (Table 3).

There were no incidences of grade 4 or worse hematologic toxicities in this study. A total of five patients (28%) experienced grade 3

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Cohort 1, Docetaxel 25 mg/m ² (n = 6)		Cohort 2, Docetaxel 30 mg/m ² (n = 6)		Cohort 3, Docetaxel 35 mg/m ² (n = 6)	
	No.	%	No.	%	No.	%
Age, years						
Mean	66.7		73.3		71.5	
SD	10.3		10.0		6.02	
Race/ethnicity						
White	6	100	3	50	6	100
Black	—		2	33	—	
Hispanic	—		1	17	—	
Bone lesions						
3-5	1	17	—		—	
6-10	—		2	33	2	33
> 10	5	83	4	67	4	67
Biochemical parameters						
Alkaline phosphatase, IU/L						
Median	158		135		160	
Range	57-972		73-199		72-1045	
PSA, ng/mL						
Median	94		150		47	
Range	35-281		7-1348		13-505	
Prior chemotherapy	6	100	5	83	5	83
Prior radiation therapy	3	50	6	100	2	33

Abbreviations: SD, standard deviation; PSA, prostate-specific antigen.

Table 2. ANC and Platelet Nadirs

Value	Cohort 1, Docetaxel 25 mg/m ²		Cohort 2, Docetaxel 30 mg/m ²		Cohort 3, Docetaxel 35 mg/m ²	
	Cycle 1 (n = 6)	Cycle 2 (n = 4)	Cycle 1 (n = 6)	Cycle 2 (n = 5)	Cycle 1 (n = 6)	Cycle 2 (n = 5)
ANC nadir, ×1,000/μL						
Median	2.0	2.1	1.7	1.6	1.7	1.7
Range	1.1-8.5	0.9-5.5	1.2-3.6	1.0-1.9	0.6-3.4	1.1-2.8
Mean	2.9	2.6	2.0	1.4	2.0	1.8
SD	2.8	2.0	0.88	0.4	1.1	0.64
Median time to nadir, days	26	34	27	14	26	14
Platelet count nadir						
Median	104	170	114	109	108	142
Range	40-235	97-289	57-194	71-200	52-243	142-405
Mean	129	168	121	118	140	165
SD	82	62	55	53	72	50
Median time to nadir, days	27	17	26	26	27	26

Abbreviations: ANC, absolute neutrophil count; SD, standard deviation.

hematologic toxicity during the study (Table 4). There was no trend toward increasing marrow toxicity with increasing docetaxel dose or after the second administration of ¹⁵³Sm. The median interval between the first and second infusion of ¹⁵³Sm-lexidronam was 35 days (range, 27 to 57 days) both overall and for each of the cohorts.

Nonhematologic Adverse Events

There were no grade 4 or worse nonhematologic toxicities related to treatment. No cohort met the criteria for DLT on the basis of

nonhematologic adverse events. The grade 3 nonhematologic adverse events observed were typical of those expected with taxane-based chemotherapy (Table 4).

PSA and Alkaline Phosphatase Levels

A total of five (28%) of the 18 patients had PSA levels decrease by at least 50% from baseline while on study. Overall, these favorable PSA responses were not related to docetaxel dose. The median time to progression for these patients was 25.6 weeks (range, 13.3 weeks to

Table 3. Effect of Prior Treatments on Nadir Levels of Neutrophils and Platelets

Variable	ANC Nadir*		PLT Nadir*	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2
All patients, n = 18				
Median	2.0	1.8	114	142
Range	0.6-8.5	0.8-5.5	40-243	71-243
Mean	2.3	2.0	133	161
SD	1.7	1.1	69	76
Prior radionuclide, n = 5				
Median	2.1	1.6	123	122
Range	1.6-3.6	1.0-1.9	57-222	75-200
Mean	2.3	1.5	141	130
SD	0.8	0.4	67	53
No prior chemotherapy, n = 2				
Median	1.4	1.4	190	189
Range	0.6-2.3	1.1-1.8	176-203	178-200
Mean	1.4	1.4	190	189
One prior chemotherapy, n = 8				
Median	1.8	1.9	114	140
Range	1.2-3.4	1.6-2.6	40-243	75-243
Mean	2.0	2.0	123	158
SD	0.7	0.4	74	65
Two prior chemotherapies, n = 8				
Median	2.3	1.7	99	112
Range	0.7-8.5	0.8-5.5	52-235	71-235
Mean	2.8	2.1	122	131
SD	2.5	1.7	64	55

Abbreviations: ANC, absolute neutrophil count; PLT, platelet count; SD, standard deviation.

*×1,000/μL.

Table 4. Adverse Events (n = 18*)

Body System	Adverse Event†	Grade 1		Grade 2		Grade 3		Grade 4	
		No.	%	No.	%	No.	%	No.	%
Blood/bone marrow	Hemoglobin	10	56	7	39	0	0	0	0
	Leukocytes, total WBC	6	33	7	39	4	22	0	0
	Neutrophils	7	39	3	17	4	22	0	0
	Platelets	7	39	4	22	1	6	0	0
Constitutional	Fatigue	3	17	7	39	3	17	0	0
GI	Constipation	4	22	2	11	0	0	0	0
	Vomiting	1	6	0	0	2	11	0	0
Musculoskeletal	Muscle weakness	1	6	0	0	0	0	1	6
Neurology	Neuropathy	3	17	2	11	0	0	1	6
Ocular/visual	Epiphora	5	28	0	0	0	0	0	0
Pain	Pain, various sites	1	6	6	33	2	11	0	0
Respiratory	Dyspnea	5	28	0	0	1	6	0	0
Genitourinary	Urinary retention	0	0	0	0	1	6	0	0

*Eighteen patients receiving 32 cycles of therapy, which consisted of 94 doses of docetaxel and 32 doses of samarium-153 lexidronam. Percentages are based on 18 patients.

†Events ≤ grade 2 are reported if they occurred in > 25% of patients, unless grade 3 or 4 toxicity was observed. All grade 3 and 4 events are included.

28.6 weeks). For all the patients, alkaline phosphatase levels reached their nadir at a median of 28 days on study and decreased by a median of 37%. One third (six of 18) of the patients had alkaline phosphatase levels decrease by at least 50% from baseline. The PSA and alkaline phosphatase responses did not always overlap; only two patients (both in cohort 3) experienced clinically relevant improvements in both PSA and alkaline phosphatase levels. At the time patients were taken off protocol, all but two had increasing PSA levels and worsening bone pains or bone scans (increased intensity or new lesions) compatible with progression of disease in the bone. Three patients had impending spinal cord compression requiring radiation therapy. Five patients also had evidence of disease progression in the lymph node. No patients developed progression of disease in a visceral organ or at the primary site.

DISCUSSION

In this study, we found that the combination of weekly docetaxel with monthly samarium ¹⁵³Sm-lexidronam was well tolerated and feasible in patients with advanced prostate cancer. Even in a patient population with significant prior chemotherapy and radiation exposure, clinically significant hematologic toxicity was rare and was not related to the docetaxel dose or repeated administration of ¹⁵³Sm-lexidronam. Nadir levels of both platelets and neutrophils were similar after the second cycle of combination treatment to those after the first cycle. The maximum-tolerated dose was not reached.

Taxane chemotherapy has become established as a front-line therapy option in CRPC. It remains to be determined whether combining taxane chemotherapy with radiopharmaceuticals is safe and feasible and whether such combination therapy would additionally improve therapeutic efficacy. A randomized phase II study has suggested that bone-targeted therapy combining anthracycline chemotherapy with a radiopharmaceutical agent provided increased time to progression and overall survival in selected patients.⁸ An updated report of the study indicated that combining radiophar-

maceuticals with chemotherapy was safe and did not affect delivery of subsequent treatments.¹⁶

Prostate cancer is a radiosensitive tumor. Jacobsson et al¹⁷ have reported that bone exposed to prior irradiation (5,000 Gy) seemed to be protected from subsequent bone metastasis in patients with poorly differentiated prostatic cancer. It remains unknown whether combining chemotherapy with radiation will enhance the inhibition of stromal/vascular elements or increase eradication of the micrometastatic cells in the bone marrow. Whether dose intensification, newer generations, or repeated dosing of radiotherapeutics and whether combining chemotherapy with radiotherapeutics will enhance antitumor effects or improve clinical efficacy require additional investigation.¹⁸⁻²¹

Currently, we do not have reliable ways to determine which patient subsets are most likely, or unlikely, to benefit from bone-targeted therapy using radiotherapeutic agents. Bone dosimetry studies suggest that low-volume skeletal metastases (< five lesions) absorb approximately 4,000 Gy of beta radiation from strontium ⁸⁹Sr chloride, moderate metastases (five to 10 lesions) absorb 8,000 Gy, and diffuse metastases absorb only 1,000 Gy.²² These results suggest that radiotherapeutics provide optimal effects on moderate metastases but repeated treatments may be necessary and advantageous for the treatment of diffuse metastases. The differential effect of radiotherapeutics on disparate tumor burden in the skeleton implies that stratification of high- versus low-volume bone disease may be important for future studies.

Optimal dose-schedules of chemotherapy combined with a radiotherapeutic have not yet been established. Results from previous studies^{10,20} suggest that patients who respond to chemotherapy are also more likely to benefit from chemotherapy combined with a radiotherapeutic agent. Hence future clinical trials using such therapeutic strategies should be designed with this caveat in mind. One plausible approach is to treat patients with a lead-in or induction chemotherapy regimen. This allows the selection of patients who have responded to an induction chemotherapy regimen for consolidation therapy using one dose or repeated treatments of radiotherapeutics.

It was of interest whether radiotherapeutics could reduce the amount of chemotherapy being given. Our results suggest that longer-term therapy with an effective dose of docetaxel is important when combined with repeated ^{153}Sm -lexidronam therapy. We found that combination therapy over an abbreviated period did not provide a durable PSA response or alkaline phosphatase improvement. All three patients who did not complete cycle 2 because of disease progression were in cohort 1 and were given the lowest dose (25 mg/m^2) of docetaxel studied. Preliminary reports by Morris et al²³ examining docetaxel up to 75 mg/m^2 every 3 weeks with ^{153}Sm -lexidronam at 1.0 mCi/kg every 9 weeks suggested that repetitive every-3-week dosing for docetaxel and every 6 to 9 weeks for ^{153}Sm was well tolerated in patients with metastatic CRPC. This dose-escalation study had not yet reached toxicity boundaries when reported. The current study taken together with the results from Morris et al will inform the dose and design of future trials with this combination regimen.

Results of the present study suggest that two dosing cycles consisting of weekly docetaxel and monthly ^{153}Sm -lexidronam were well tolerated and feasible in this CRPC population. An effective duration and dosage of chemotherapy may be required for potential synergistic interactions between the cytotoxic docetaxel and the bone-targeting

^{153}Sm . Additional prospective, randomized studies need to be performed to determine whether this combination can affect patient survival and quality of life in a favorable manner.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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