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Dose-finding Study of ^{153}Sm -EDTMP in Patients With Poor-prognosis Osteosarcoma

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Abstract

BACKGROUND—Samarium-153 ethylenediaminetetramethylene phosphonic acid (^{153}Sm -EDTMP) has been used to treat patients with high-risk osteosarcoma. The purpose of the current study was to determine the maximally tolerated dose of ^{153}Sm -EDTMP that permits hematopoietic recovery within 6 weeks.

METHODS—Patients with recurrent or refractory osteosarcoma with bone metastases were enrolled in this study. Subjects were treated with increasing doses of ^{153}Sm -EDTMP, beginning with 1.0 millicuries (mCi)/kg and followed initially with 40% increment dose level escalations, using a continual reassessment method for dose escalation and de-escalation with a target dose-limiting toxicity (DLT) rate of 30%. Complete blood counts were monitored weekly, and the primary DLT was defined as failure to achieve an absolute neutrophil count $>750/\text{mm}^3$ and a platelet count $>75,000/\text{mm}^3$ within 6 weeks of treatment. In addition to assessing toxicity, dosimetry measurements were made to estimate the radiation dose delivered to target lesions.

RESULTS—The maximally tolerated dose of ^{153}Sm -EDTMP was 44.8 megabecquerel (MBq)/kg (1.21 mCi/kg). DLTs were confined to hematologic toxicities, particularly delayed platelet recovery in 2 patients treated at a dose of 51.8 MBq/kg (1.4 mCi/kg). Grade 2 and 3 pulmonary toxicity (graded according to the National Cancer Institute Common Toxicity Criteria [version 3.0]) as reported in 2 patients (at administered activities of 44.8 MBq/kg and 51.8 MBq/kg) was attributable to progressive pulmonary disease. No other significant nonhematologic toxicities were observed.

CONCLUSIONS—Patients with osteosarcoma who have previously been heavily treated with chemotherapy can be safely administered ^{153}Sm -EDTMP with rapid hematologic recovery. The data from the current study support the development of a future trial to assess the efficacy of combining

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targeted radiotherapy with cytotoxic chemotherapy as a treatment option for patients with high-risk osteosarcoma.

Keywords

radiopharmaceuticals; targeted radiotherapy; osteosarcoma; bone neoplasm

Osteosarcoma is the most common primary malignant tumor of bone diagnosed in children and adolescents. The combination of chemotherapy and aggressive surgery can cure up to 75% of patients with localized disease, in contrast to patients with high-risk disease (defined as that found to be metastatic at presentation, especially to distant bony sites; refractory to chemotherapy; or unable to be completely resected), whose cure rate is reported to be <15%.¹ Although there was a tremendous improvement in overall patient survival reported with the introduction of effective chemotherapy, subsequent dose intensification appears to have been of no benefit to patients with high-risk disease and therefore new treatment approaches are clearly needed.

Osteosarcoma is a relatively radioresistant tumor. Doses of <60 grays (Gy) are associated with only transient tumor control, and even when using doses of ≥ 80 Gy, viable tumor has been found in amputation specimens.^{2–4} This finding has limited the applicability of radiotherapy in this disease, because such doses are associated with significant normal tissue injury. Recent studies, however, have indicated that lower dose radiotherapy can assist in providing local control of osteosarcoma for patients with marginal resections.⁵ This finding supports the development of chemoradiotherapy treatment protocols for patients with high-risk disease, especially if treatment can be targeted directly to the tumor rather than to surrounding normal tissue.

Samarium-153 ethylenediaminetetramethylene phosphonic acid (¹⁵³Sm-EDTMP) is a bone-seeking radiopharmaceutical designed to selectively deliver radiation to osteoblastic skeletal metastases.⁶ The radioisotope ¹⁵³Sm emits an electron (beta particle) with an average energy of 224 kiloelectron volts (keV) (approximate range of 0.5 mm), which is appropriate for targeted cytotoxicity. Its photon emissions include a 103-keV photon appropriate for scintigraphic imaging, thereby allowing both confirmation of localization of the agent and quantification of the radiation delivered to target lesions. ¹⁵³Sm has a half-life of 47 hours, allowing therapy to be delivered safely in the outpatient setting.

¹⁵³Sm-EDTMP has been used for the treatment of high-risk osteosarcoma. A phase 1 study found that up to 11.1 gigabecquerels (GBq)/kg (30 millicuries [mCi]/kg) could be administered with autologous stem cell support; the only significant toxicity was myelosuppression.⁷ In an effort to improve efficacy, Anderson et al combined a dose of 11.1 GBq/kg ¹⁵³Sm-EDTMP with gemcitabine as a radiation sensitizer.⁸ Although some patients achieved partial responses, none of the responses were durable. The approach of combining chemotherapy with a radiopharmaceutical requires a clear understanding of the kinetics of hematopoietic recovery after treatment with ¹⁵³Sm-EDTMP.

The primary goal of the current study was to identify a dose of ¹⁵³Sm-EDTMP that would allow hematopoietic recovery within 6 weeks without use of stem cell support. Six weeks was chosen so that myelosuppression related to ¹⁵³Sm-EDTMP administration would not cause prolonged treatment delays when combined with chemotherapy. Secondary goals included the evaluation of the efficacy of low dose ¹⁵³Sm-EDTMP for patients with high-risk osteosarcoma and quantification of the adsorbed dose delivered to target lesions by this treatment.

MATERIALS AND METHODS

Eligibility Requirements

Eligible patients were aged <40 years, with biopsy-proven high-risk osteogenic sarcoma (defined as recurrent after conventional therapy, unresectable, or newly diagnosed disease with bone metastases or >4 pulmonary metastases) that was detectable on a standard technetium 99m bone scan. Adequate renal and hematologic function were required (including an absolute neutrophil count [ANC] of $\geq 1000/\text{mm}^3$ and a platelet count $\geq 100,000/\text{mm}^3$). Informed consent was obtained according to institutional policies. Patients were excluded if they had a Karnofsky performance status <50%, had clinically significant cardiac disease, were pregnant or breast-feeding, had received prior radiotherapy for osteosarcoma, or had prior radio-therapy for any other reason within the preceding 6 months. Patients with a prior malignancy must have been in remission for at least 5 years.

Treatment Plan and Dose Modifications

^{153}Sm -EDTMP was administered intravenously in the Radiation Oncology outpatient clinic. The first dose level, 37 megabecquerel (MBq)/kg (1.0 mCi/kg), is the US Food and Drug Administration (FDA) -approved dose for the palliation of bone metastases. The second dose level was a 40% increase, 51.8 MBq/kg (1.4 mCi/kg). Subsequent dose levels were to be sequential 40% increases until toxicity was observed. When toxicity was first noted, a dose-response curve was estimated based on the observed data; further doses were then determined by the continuous reassessment method (CRM)⁹ using a target frequency of toxicity at the maximum tolerated dose (MTD) of 30%. Patients were enrolled in cohort sizes of 2, and the CRM algorithm was applied after each pair of patients was evaluated. The primary dose-limiting toxicity (DLT) was expected to be failure of hematopoietic recovery, defined as an ANC $< 750/\text{mm}^3$ and a platelet count $< 75,000/\text{mm}^3$ within 6 weeks. Grade 3 or 4 non-hematologic toxicities attributable to drug administration were also considered to be DLTs.

When the first DLT was encountered, the dose-response curve was estimated using a 1-parameter logistic model (ie, toxicity as a function of administered activity). Using the curve, we found the administered activity that is most consistent with 30% toxicity and defined this as the next dose level (Fig. 1). The specific form of the CRM model was suggested by Goodman et al.⁹

$$p(\text{toxicity}|\text{dose}=d_i) = \frac{\exp(3 + \alpha[0.74d_i - 6.62])}{1 + \exp(3 + \alpha[0.74d_i - 6.62])}$$

In the dose-toxicity model above, the model is estimated using a maximum likelihood approach.

Secondary outcomes were assessed by descriptive statistics, including the proportion of subjects with an objective response to therapy and the adsorbed dose to the target lesions. Other toxicities were assessed by the National Cancer Institute Common Toxicity Criteria (version 3.0). Adsorbed dose was compared using a 2-sample Student *t* test after taking a log-transform of the data to achieve a symmetric distribution. Mean and 95% confidence intervals were estimated. Kaplan-Meier estimation was used to describe time to tumor progression.

Radiation Dosimetry

^{153}Sm -EDTMP scans were performed 4 hours after infusion, and again 24 to 48 hours later using a standard scintigraphic camera and an acquisition window centered around the 103 keV

photopeak. Anterior/posterior whole-body sweeps were performed at a detector speed of 8 to 10 cm/minute with no contouring. The Medical Internal Radiation Dose (MIRD) Committee formalism was used, as implemented in the OLINDA software package.¹⁰ The measured lesion activity concentration was adjusted to account for detector count rate saturation (Siegel et al¹¹ and unpublished data) to calculate the absorbed doses to target lesions and normal bone.

Response Evaluation

Before treatment, patients were evaluated with a computed tomography (CT) scan of the chest, CT or magnetic resonance imaging (MRI) of the primary tumor, and a bone scan. At the time of hematologic recovery, these imaging studies were repeated. Radiographic response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria: partial response indicated a >50% reduction in the sum of the products of perpendicular tumor dimensions; a minor response indicated a 25% to 50% reduction in the sum of the products of the tumor dimension without the emergence of new lesions, and no individual lesion progressing >25% in a single dimension; stable disease indicated no progressive disease; and progressive disease indicated the emergence of new lesions or the progression of any lesion by >25% in a single dimension. An objective response was defined as stable disease or better.

RESULTS

Patient Characteristics

Thirteen subjects were enrolled in this dose-finding study (Table 1). The median age was 14 years (range, 6–30 years). A total of 11 patients had high-grade osteoblastic osteosarcoma, 1 patient had chondroblastic osteosarcoma, and 1 patient had a giant-cell-rich grade 2 osteosarcoma. Five patients had primary refractory disease, with disease progression occurring during chemotherapy; 4 patients were treated at the time of first disease recurrence (2 of whom were refractory to rescue chemotherapy), and 4 patients were treated at the time of second or subsequent disease recurrence. All of the patients were heavily pre-treated with chemotherapy. All had received methotrexate, cisplatin, and doxorubicin; 11 had also received at least ifosfamide and etoposide. In addition, 3 patients had been treated with gemcitabine with or without taxotere, and 1 patient had received high-dose chemotherapy with autologous peripheral blood stem cell transplantation.

A total of 12 of the patients had bony lesions identifiable on standard bone scan; 7 also had pulmonary lesions that were not visible on bone scan. One patient had disease limited to the lungs, but these lesions were readily visible on bone scan. At the time of treatment, 2 patients had pleural effusions, 1 of whom also had cardiomyopathy and the other renal Fanconi syndrome.

Toxicities

The DLT was thrombocytopenia for 4 patients, 2 of whom also experienced dose-limiting neutropenia (Table 2). The MTD, as calculated by the CRM algorithm, was 44.8 MBq/kg (1.21 mCi/kg). This was 20% higher than the FDA-approved dose for palliation. Our CRM algorithm incorporated a target DLT rate at the MTD of 30%. The 90% confidence interval for the DLT rate at the dose of 44.8 MBq/kg was 15% to 54%.

Toxicity attributable to treatment was limited to the hematopoietic system, and platelets were most profoundly affected (Table 2). Of the 12 evaluable patients, 8 experienced either grade 3 or grade 4 thrombocytopenia, with a nadir reached during Week 4 after treatment. Thrombocytopenia accounted for 4 DLTs. Platelet counts for these patients at Week 6 were 46,000/ μ L, 57,000/ μ L, 20,000/ μ L, and 7000/ μ L. For 3 of the patients, thrombocytopenia resolved by Week 8. The fourth patient (with a platelet count of 7000/ μ L) entered hospice care

and had no further blood draws. Neutropenia was variable and usually resulted in a neutrophil nadir during Week 4. Three patients had grade 1 or 2 neutropenia and 5 patients had grade 3 or 4 neutropenia. There were 2 DLTs due to neutropenia, both in patients who also experienced a DLT due to thrombocytopenia. For these patients, absolute neutrophil counts were 36/ μ L and 260/ μ L at Week 6. Both patients had resolution of their neutropenia by Week 8. Anemia was generally mild, with 11 of 12 evaluable patients experiencing only grade 1 or 2 anemia. No red blood cell transfusions were required.

Only 2 patients experienced significant nonhematopoietic toxicity. One patient experienced an increase in the size of a pleural effusion, with increasing pleuritic chest pain and dyspnea (Patient 3, who was given other disease-directed therapy before count recovery and therefore was unevaluable for hematologic recovery). These symptoms were caused by progressive disease, and were not attributable to treatment. Another patient had asymptomatic grade 3 hyponatremia that resolved spontaneously. Most patients experienced a transient increase in pain at the site of bony lesions, beginning 24 to 48 hours after treatment, lasting 24 to 48 hours, and responding to oral pain relievers such as acetaminophen.

Dosimetry

Visualization of ^{153}Sm -EDTMP uptake provided confirmation of drug delivery to target lesions and allowed calculation of the tumor adsorbed dose. Evaluable dosimetry data were available for 16 distinct lesions in 9 of the patients. The tumor adsorbed dose varied from 0.9 to 21.4 Gy (Table 3). Despite this wide range, there was no significant correlation noted between administered activity and tumor adsorbed dose (Fig. 2 Top). The adsorbed dose also did not correlate with tumor size (data not shown). Surprisingly, we found that the tumor adsorbed dose appeared to vary more between patients than between tumors, with some patients having tumors that appeared to have much greater avidity for ^{153}Sm -EDTMP than others (Fig. 2 Bottom).

Disease Response

Although it is used for palliation of painful bone metastases, the goal of treating osteosarcoma patients with ^{153}Sm -EDTMP is to provide cytotoxic therapy. Therefore, we measured response to therapy radiographically. No patients achieved a radiographic complete or partial response as defined by RECIST criteria. However, radiographic response of osteosarcoma is extremely difficult to measure because the tumor is calcified. Newly diagnosed disease, even that with >95% necrosis, often demonstrates minimal radiographic change. Some even demonstrate increased tumor size despite excellent necrosis.

Of the 13 evaluable patients, 5 (38%) had stable disease at the end of the study (6 weeks after treatment), and the other 8 had disease progression. Assessment of durability of response was not possible, because the majority of patients went on to receive further therapy: 6 of the patients received a second, higher dose of ^{153}Sm -EDTMP with autologous hematopoietic stem cell support and 2 received further chemotherapy. Nevertheless, as calculated using a Kaplan-Meier analysis, the median time to disease progression was 51 days (Fig. 3), and 3 patients survived for a significant period of time after treatment. One of these patients, with a low-grade, giant-cell-rich osteosarcoma of the clivus that was metastatic to the bilateral taluses, survived for 1 year after treatment. Two patients who were treated for widely metastatic, primary refractory disease remained alive (with active disease) at the time of last follow-up, 24 months and 41 months, respectively, after treatment. These 2 survivors were also treated with a second, higher samarium dose requiring autologous peripheral blood stem cell support as well as aggressive surgery.

No correlation between tumor adsorbed dose and disease stabilization was noted (Fig. 4). The mean tumor adsorbed doses were not found to be significantly different between patients with stable disease (2.69 Gy) and patients with progressive disease (6.71 Gy), as judged by the Student *t* test for unpaired data ($P = .115$). To our knowledge, the factors that affect tumor avidity for and sensitivity to ^{153}Sm -EDTMP remain to be identified. The 2 patients with nonosteoblastic morphology were among the 5 to achieve disease stabilization, but it is not clear if this finding reflects a particular sensitivity of these subtypes. Another related question is whether ^{153}Sm -EDTMP is effective in patients with micrometastatic disease. Of the 8 patients with progressive disease in the current study, only 2 had distant failures, whereas 6 had their disease progression manifest as enlargement of existing lesions (local failure). This pattern of failure suggests the possibility that this treatment might have some effect on tumor micrometastases.

DISCUSSION

In the current study, we report the results of a dose-finding study of ^{153}Sm -EDTMP. Our dose-finding algorithm was designed to identify a dose of ^{153}Sm -EDTMP that would have a DLT rate of 30%, with the DLT defined as failure of hematologic recovery within 6 weeks. We found this dose to be 44.8 MBq/kg (1.21 mCi/kg). Even in this heavily pretreated population, this level of radioactivity could be safely administered without undue hematologic toxicity, and, in keeping with previous reports, there were no significant nonhematologic drug-related toxicities attributable to treatment. Thus, it should be feasible to develop treatment regimens that combine chemotherapy with ^{153}Sm -EDTMP for patients with bone metastases.

Our study design used the CRM to determine the MTD. The CRM was first introduced by O'Quigley et al in 1990.¹² The version we implemented was described by Goodman et al.⁹ This method has been demonstrated by statistical simulation to be less biased and more efficient for estimating MTD than ad hoc dose ranging methods such as the Fibonacci scheme.¹³

Although not a primary objective of this dose-finding study, treatment response was evaluable in 13 patients. We noted an objective response rate of 38% (5 of 13 patients), despite treating a population that was comprised entirely of patients with refractory, progressive disease. Three of the patients survived for >1 year. We also determined the pattern of failure of the patients who did not respond to therapy, and found that only 2 of those 8 patients had distant failures. This finding suggests that ^{153}Sm -EDTMP might have efficacy against micrometastatic disease, despite the inability to detect such disease on a standard bone scan. Given the low toxicity of this treatment and the ability to administer repeated doses, these features raise the possibility that ^{153}Sm -EDTMP could be tested as a "maintenance" drug to prolong disease-free survival in high-risk patients.

There was no obvious correlation noted between the administered activity and the tumor adsorbed dose. However, the range of administered activities investigated in this study was relatively narrow. There was also no obvious correlation found between tumor adsorbed dose and response to treatment. We did, however, recognize 2 distinct populations of tumors: tumors from 3 of our patients (Patients C, G, and H from Fig. 2 Bottom) had almost no ^{153}Sm uptake, whereas significant, although variable, uptake was noted in the other tumors. It is interesting to note that Patient C experienced disease stabilization and was alive and in disease remission at the time of last follow-up, 41 months after treatment.

In summary, we determined that a dose of 44.8 MBq/kg of ^{153}Sm -EDTMP can be delivered to heavily pretreated patients with predictable hematopoietic toxicity. The results of the current study further demonstrated that this agent can be effective in the treatment of patients with high-risk osteosarcoma. Future work will focus on better understanding the factors that

contribute to drug delivery and on improving efficacy by combination with chemotherapy, biologics, or external beam radiotherapy.

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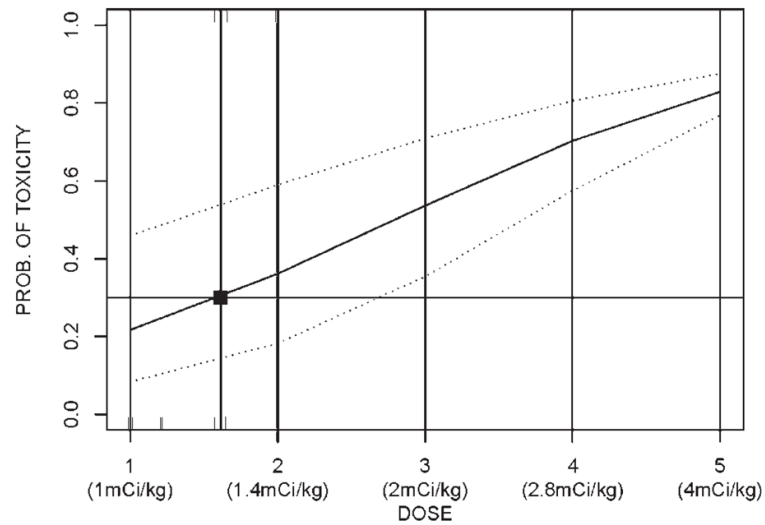


FIGURE 1.

The continuous reassessment model. The heavy line indicates the relation between administered activity (x axis) and probability (PROB) of toxicity (y axis) as calculated by the formula given in the text. The dotted lines indicate the 90% confidence intervals. The square indicates the dose that corresponds to the predicted toxicity rate of 30%, which was the target of the model.

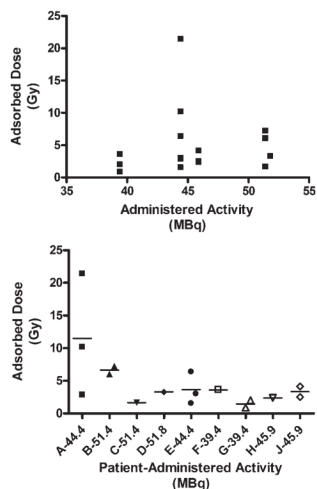


FIGURE 2. Relation between administered activity and adsorbed dose. (*Top*) The tumor adsorbed dose was measured for several lesions in each patient and compared with the dose of samarium-153 ethylenediaminetetramethylene phosphonic acid ($^{153}\text{Sm-EDTMP}$) administered to the patient. Each data point represents an individual lesion. (*Bottom*) Tumor adsorbed dose compared with administered activity presented by patient. The letters A–I designate individual patients, and the activity administered to each patient is presented next to the patient’s identifying letter. Each symbol represents an individual lesion, and the small horizontal line indicates the mean tumor adsorbed dose for that patient. Gy indicates grays; MBq, megabecquerel.

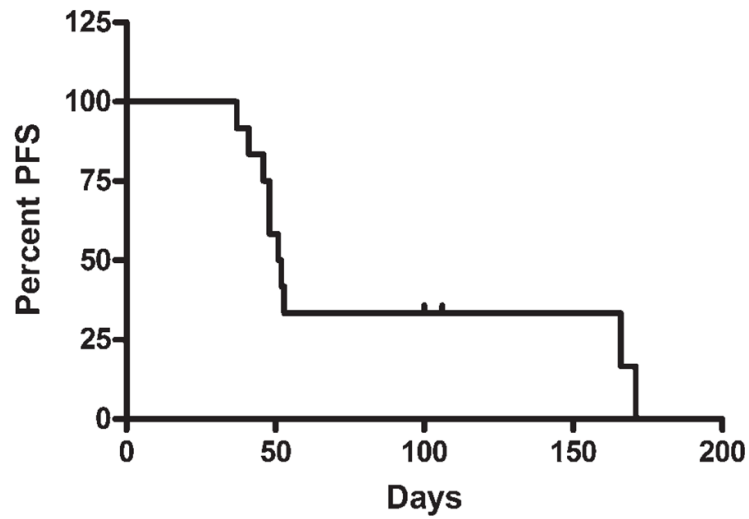


FIGURE 3. Time to disease progression. A Kaplan-Meier survival curve indicating the number of days from the pretreatment evaluation until the first evaluation that demonstrated radiographic evidence of progressive disease is shown. PFS indicates progression-free survival.

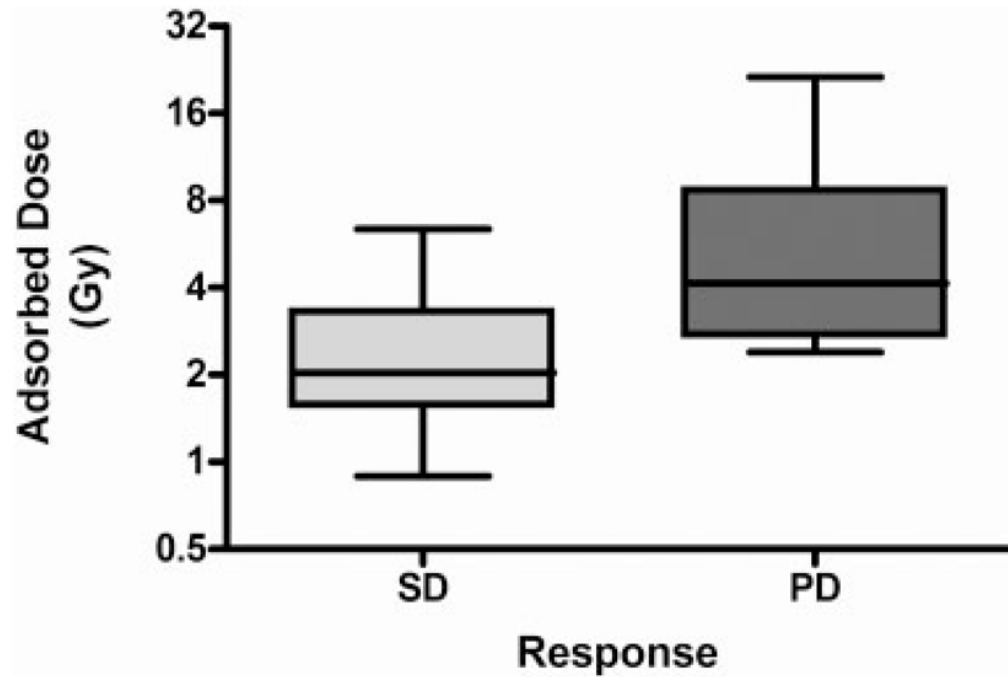


FIGURE 4. Correlation between adsorbed dose and tumor response. The median and range of tumor adsorbed doses for the patients who experienced stable disease (SD) are compared with the median and range of tumor adsorbed doses for the patients who experienced progressive disease (PD). Gy indicates grays.

Table 1

Patient Demographics

Patient No.	Gender	Age	Pathology	Disease Status	Disease Sites	Previous Treatment	Other Medical Problems
1	F	8 y, 11 mo	Chondroblastic	Recurrence 1	Right lung, Right 8th rib	Cisplatin/dox/MTX/etoposide/ifos	—
2	M	8 y, 5 mo	Low-grade osteosarcoma (2 of 3), giant cell rich	Refractory recurrence 1	Clivus, bilateral taluses	Cisplatin/dox/MTX	—
3	M	14 y, 2 mo	High-grade osteoblastic	Recurrence 1	Bilateral pulmonary nodules	Cisplatin/dox/MTX/etoposide/ifos	Pleural effusion, renal Fanconi syndrome
4	F	18 y, 7 mo	High-grade osteoblastic	Recurrence 2	L2 vertebral body, left lung	Cisplatin/dox/MTX	—
5	M	11 y, 6 mo	High-grade osteoblastic	Primary refractory	Pelvis, lungs, ribs, scapula	Cisplatin/dox/MTX/etoposide/ifos	—
6	M	17 y, 6 mo	High-grade osteoblastic	Primary refractory	Lungs, inguinal lymph nodes	Cisplatin/dox/MTX/etoposide/ifos	—
7	F	30 y, 9 mo	High-grade osteoblastic	Recurrence 4	Chest wall	Cisplatin/doxo/MTX; gemcitabine/docetaxel; ifos	—
8	M	15 y, 5 mo	High-grade osteoblastic	Primary refractory	Ribs, spine, right knee	Cisplatin/doxo/MTX/etoposide/ifos	—
9	F	14 y, 3 mo	High-grade osteoblastic	Recurrence 3	Left lung, skull, patella, pelvis	Cisplatin/doxo/MTX/etoposide/ifos	—
10	M	21 y, 4 mo	High grade	Refractory recurrence 1	Left chest wall, right lung, ribs, sternum, thoracic spine, iliac spine	Cisplatin/doxo/MTX/etoposide/ifos	Pleural effusion, cardiomyopathy, recent pulmonary embolus
11	M	12 y, 7 mo	High-grade osteoblastic	Primary refractory	Skull, sternum, right humerus, right scapula, thoracic spine, pelvis, bilateral femurs, right fibula, left tibia	Cisplatin/doxo/MTX/etoposide/ifos; mel/thiolepa; bleo/cyclo/actino; zoledronic acid	—
12	M	21 y, 2 mo	High grade	Recurrence 2	Right upper lobe of lung, L4 and S1 vertebral bodies, right ilium, retroperitoneal soft tissue	Cisplatin/doxo/MTX/etoposide/ifos; gemcitabine	Asthma

Patient No.	Gender	Age	Pathology	Disease Status	Disease Sites	Previous Treatment	Other Medical Problems
13	F	6 y, 9 mo	High-grade osteoblastic	Primary refractory	Left iliac crest, T2, T10, left scapula, bilateral femurs	Cisplatin/doxo/MTX/etoposide/ifos; gemcitabine/docetaxel	—

F indicates female; dox, doxorubicin; MTX, methotrexate; ifos, ifosfamide; M, male; Mel, melphalan; bleo, bleomycin; cyclo, cyclophosphamide; actino, actinomycin.

Table 2

Toxicities* and Response

Patient No.	Dose Level	Dose Delivered, mCi/kg	Time to Recovery, Weeks		Hematologic Toxicity Grade			Treatment Response	Other Toxicities
			ANC	Platelets	ANC	Hgb	Platelets		
1	1	1.00	NA	6	0	1	2	SD	—
2	1	1.00	NA	NA	0	2	1	SD	—
3	2	1.40	NE	NE	—	—	—	PD	—
4	2	1.40	NA	DLT	3	2	3	SD	—
5	2a	1.39	NA	6	2	2	3	PD	Pleural effusion with pleuritic pain and dyspnea
6	2a	1.39	DLT	DLT	4	2	4	SD	—
7	2b	1.20	6	6	3	2	3	PD	—
8	2b	1.20	DLT	DLT	3	1	4	SD	—
9	2c	1.065	NA	5	3	2	3	PD	—
10	2c	1.065	NA	6	0	3	2	SD	—
11	2d	1.24	NA	6	0	1	2	PD	—
12	2d	1.24	NA	4	2	1	3	PD	—
13	2d	1.24	NA	DLT	0	1	4	PD	Grade 3 hyponatremia

ANC, absolute neutrophil count; Hgb, hemoglobin; NA, not applicable (counts never fell below target for recovery); SD, stable disease; NE, not evaluable (patient taken off study prior to recovery); PD, progressive disease; DLT, dose-limiting toxicity (patient's counts did not recover in time).

* Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Table 3

Dosimetry*

Patient No.	Lesion	Administered Activity, MBq/kg	Adsorbed Dose, Gy	Response
4	L2 vertebra	51.8	3.31	SD
5	Shoulder	51.4	7.23	SD
5	Hip	51.4	6.05	SD
6	Pelvic lymph node	51.4	1.66	SD
7	Sternum	44.4	21.4	PD
7	Chest wall	44.4	10.2	PD
7	Abdomen	44.4	2.89	PD
8	L1 vertebra	44.4	3.01	SD
8	Femur	44.4	6.38	SD
8	Femur	44.4	1.55	SD
9	Paraspinal	39.4	3.61	PD
10	Left chest	39.4	0.89	SD
10	Right chest	39.4	2.03	SD
11	Knee	45.9	2.39	PD
12	Spine	45.9	4.14	SD
12	Hip	45.9	2.50	SD

MBq indicates megabecquerel; Gy, grays; SD, stable disease; PD, progressive disease.

* For each listed patient, dosimetry was performed as described for 1 or more lesions.