High-Dose Samarium-153 Ethylene Diamine Tetramethylene Phosphonate: Low Toxicity of Skeletal Irradiation in Patients With Osteosarcoma and Bone Metastases

By Peter M. Anderson, Gregory A. Wiseman, Angela Dispenzieri, Carola A.S. Arndt, Lynn C. Hartmann, William A. Smithson, Brian P. Mullan, and Oyvind S. Bruland

Purpose: **Samarium-153 ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), a bone-seeking radiopharmaceutical, provides therapeutic irradiation to osteoblastic bone metastases. Because the dose-limiting toxicity of ^{153}Sm-EDTMP is thrombocytopenia, a dose-escalation trial using peripheral-blood progenitor cells (PBPCs) or marrow support was conducted to treat metastatic bone cancer.**

Patients and Methods: **Patients with locally recurrent or metastatic osteosarcoma or skeletal metastases avid on bone scan were treated with 1, 3, 4.5, 6, 12, 19, or 30 mCi/kg of ^{153}Sm-EDTMP.**

Results: **Thirty patients were treated with ^{153}Sm-EDTMP. Transient symptoms of hypocalcemia were seen at 30 mCi/kg. Estimates of radioisotope bound to bone surfaces and marrow radiation dose were linear with injected amount of ^{153}Sm-EDTMP. Cytopenias also occurred in all subjects and were dose-related. At day +13 after ^{153}Sm-EDTMP, residual whole-body radioactivity was 1% to 65% of whole-body radioactivity considered safe for PBPC infusion, 3.6 mCi. After PBPC or marrow infusion on day +14 after ^{153}Sm-EDTMP, recovery of hematopoiesis was problematic in two patients at the 30 mCi/kg dose infused with less than 2×10^6 CD34$^+$/kg on day +14, but not in other patients. Reduction or elimination of opiates for pain was seen in all patients. Patients had no adverse changes in appetite or performance status.**

Conclusion: **^{153}Sm-EDTMP with PBPC support can provide bone-specific therapeutic irradiation (estimates of 39 to 241 Gy). Hematologic toxicity at 30 mCi ^{153}Sm-EDTMP/kg requires PBPC grafts with more than 2×10^6 CD34$^+$/kg to overcome myeloablative effects of skeletal irradiation. Nonhematologic side effects are minimal.**

J Clin Oncol 20:189-196. © 2001 by American Society of Clinical Oncology.

RADIOISOTOPES WITH medium-energy beta emission and half-life of a few days are attractive candidates for systemic delivery of targeted irradiation.[1] Bone metabolism involved in homeostatic structural maintenance as well as response to neoplasia permits selective uptake and retention of phosphonate complexes in bone metastases and bone-forming tumors such as osteosarcoma. Samarium (Sm)-153 is easily produced by neutron capture from ^{152}Sm to yield a radioisotope of high purity with both medium-energy beta emission for therapeutic purposes and gamma emission useful for conventional gamma camera scintigraphic imaging. Work by Goeckler et al[2] showed that ^{153}Sm ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), a tetra phosphonate chelate with high specific activity, is easily prepared. ^{153}Sm-EDTMP has high bone uptake. Although bone surfaces retain ^{153}Sm-EDTMP for months, unbound ^{153}Sm-EDTMP has rapid blood clearance into the urine.[3] Compared with technetium-99m methylene diphosphonate (^{99m}Tc-MDP) preparations used for routine bone imaging or ^{99m} Tc-EDTMP, ^{153}Sm-EDTMP has comparable or better bone/blood and bone/muscle ratios.[3,4] Because of these very favorable bone-seeking characteristics, ^{153}Sm-EDTMP was developed as an agent for palliative treatment of bone metastases. The United States Food and Drug Administration approved ^{153}Sm-EDTMP in April 1998 for pain palliation in patients with bone metastases; a standard palliative dose is 1 mCi/kg.

Also, a bone-forming tumor such as osteosarcoma often has avid uptake of bone-seeking radiopharmaceuticals such as ^{153}Sm-EDTMP. Large dogs with spontaneous osteosarcoma have been treated with ^{153}Sm-EDTMP, with tumor to normal bone ratios of 5 to 10 and tumor to lung ratios of 100 to 300.[5,6] Avidity of ^{99m}Tc-MDP predicted selectivity of ^{153}Sm-EDTMP uptake. In one report seven of 40 dogs with osteosarcoma had durable remissions.[5] Temporary thrombocytopenia (platelets $<$ 20,000) was seen in canine studies at 2 mCi/kg.[7] However, even at 30 mCi of ^{153}Sm-EDTMP/kg, which was estimated to deliver 30 Gy to the red marrow

From the Mayo Clinic, Rochester, MN; and Norwegian Radium Hospital, Oslo, Norway.

Submitted November 17, 2000; accepted July 31, 2001.

Supported by the Wasie Foundation, the Van der Steen Foundation, and Mayo Clinic GCRC.

Address reprint requests to Peter M. Anderson, MD, PhD, Mayo Clinic, Department of Pediatrics, 200 First St SW, Rochester, MN 55905; email: anderson.peter@mayo.edu.

0732-183X/01/2001-189/$20.00

of dogs given ^{153}Sm-EDTMP, spontaneous recovery of hematopoiesis sometimes occurred.[8]

Humans have pancytopenia after ^{153}Sm-EDTMP.[9-12] Despite somewhat variable binding of ^{153}Sm-EDTMP to bone and bone surfaces in humans (40% to 95% of an injected dose[9]), less than 1% of an injected dose remains in nonosseous tissues after rapid bone uptake and urinary excretion. Thus effect of radiation on the red marrow is the dose-limiting toxicity of ^{153}Sm-EDTMP. So far there are no reports of ^{153}Sm-EDTMP as primary treatment of osteosarcoma in humans, but treatment of locally relapsing and metastatic osteosarcoma has been effective in some cases.[11,12] In an effort to learn more about toxicity and whether patients with bone metastases or osteosarcoma could safely benefit from higher doses of ^{153}Sm-EDTMP, we studied the use of escalating doses of ^{153}Sm-EDTMP followed by peripheral-blood progenitor cell (PBPC) or marrow support.

PATIENTS AND METHODS

Study Population

Subjects with bone metastases or osteosarcoma metastases easily identifiable on ^{99m}Tc bone scan were treated. All patients had experienced treatment failure with prior standard therapies, and no curative therapy was available for their disease. Table 1 lists clinical characteristics. All patients or legal guardians were appraised of indications, risks, and alternatives and provided informed consent. To receive high-dose ^{153}Sm-EDTMP, a source of autologous, cryopreserved hematopoietic progenitor cells was required. Although this may not have been necessary at the 3 mCi/kg dose, the very heavily pretreated nature of these patients and limited stem-cell reserve made it necessary to adopt the use of PBPC for all patients treated with doses exceeding the standard 1 mCi/kg dose. PBPC or bone marrow (n = 1) was collected at Mayo Clinic or the referring institution. In some patients, mobilization failed to yield an adequate number of PBPCs (> 10/mL) and it was not possible to collect marrow because of metastatic disease. These subjects were not eligible for high-dose ^{153}Sm-EDTMP and

Table 1. Clinical Characteristics of Patients With Osteosarcoma or Bone Metastases

Dose Level (mCi/kg)	Age (years)	PS	Pain	Bone Malignancy	Osteoblastic Bone Metastasis*
1	18	0	Yes	OGS	**Femur**, mediastinum, lungs
1	16	0	Yes	OGS	**Humerus**, ribs
1	12	1	Yes	OGS	**Spine**, ribs, pelvis, lungs
1	15	1	Yes	OGS	**Tibia**, rib, lungs
3	16	0	No	Adenocarcinoma	**Femur**, spine; ribs, tibia, pelvis
3	18	2	Yes	OGS	**Femur**, L5, clavicle, lungs, pelvis
3	18	1	Yes	OGS	**Mediastinum**, kidney, sternum, ribs
4.5	57	1	Yes	Breast cancer	**Sternum**, spine, ribs
4.5	55	1	Yes	Breast cancer	**Femur**, skull, clavicle, ribs
4.5	45	1	Yes	Breast cancer	**Femur**, humerus, ribs, spine, pelvis
6	20	0	No	OGS	**Mandible**
6	19	0	Yes	OGS	**Humerus**, rib, spine, sacrum, tibia
6	35	1	Yes	Paraganglioma	**Sternum**, clavicles, humeri, spine
12	11	0	No	OGS	**Lungs** (TNTC)
12	12	2	Yes	OGS	**Pelvis**, femur, ribs, skull, lungs (TNTC)
19	46	1	Yes	Chondrosarcoma	**Pelvis**, sacrum, L5 spine
30	19	0	Yes	OGS	**Skull** (2)
30	33	1	Yes	OGS	**Manubrium**, right shoulder
30	43	1	Yes	OGS	**Femur**, pelvis, spine, right humerus
30	16	1	No	OGS	**Humerus**
30	21	0	Yes	OGS	**Femur**
30	9	0	Yes	OGS	**Pleural rind**, lungs (TNTC)
30	19	1	Yes	OGS	**Spine**
30	24	2	Yes	OGS	**Femur**, pelvis, spine, ribs, skull, lungs
30	15	0	Yes	OGS	**Tibia**, distal femur
30	16	2	Yes	OGS	**Pelvis**, lungs
30	24	0	Yes	OGS	**Spine**, mediastinum
30	15	0	Yes	OGS	**Humerus**
30	29	0	Yes	Paraganglioma	**Spine**, shoulder
30	16	0	No	OGS	**Maxilla**

Abbreviations: PS, Eastern Cooperative Oncology Group performance status; bone pain, severe pain from bone metastases requiring opiates; OGS, osteogenic sarcoma; TNTC, too numerous to count metastases.

*Bold indicates indicator lesion.

received either palliative care (n = 1; this patient also had therapy-related leukemia) or standard-dose ^{153}Sm-EDTMP (1 mCi/kg; n = 4).

Treatment Schema

Figure 1 illustrates the sequence of treatment. Initially, three dose levels of ^{153}Sm-EDTMP were evaluated: 3 mCi/kg, 4.5 mCi/kg, and 6 mCi/kg (n = 3/cohort). Because of slow accrual (2 years to accrue nine patients) and lack of funds to facilitate timely PBPC collection, a parallel clinical trial in patients with multiple myeloma at 6, 12, 19, and 30 mCi/kg was conducted (n = 3/cohort[13]). This trial yielded safety and dosimetry data that showed lack of toxicity and relatively high-dose estimates of marrow irradiation at the highest dose (up to 40 Gy). During this trial, a small number of patients with osteosarcoma (12 mCi/kg; n = 2) or osteoblastic chondrosarcoma bone metastases (19 mCi/kg; n = 1) were treated at intermediate doses after safety had been demonstrated in a separate study involving patients with multiple myeloma.[13] The maximum-tolerated dose (MTD) for a 30-minute infusion was reached in the myeloma study at 30 mCi/kg, with occurrence of transient hypocalcemia. Additional logistic considerations, including poor engraftment in two of 13 patients and the amount of radioisotope to be shipped and handled, influenced the decision to adopt 30 mCi/kg as the highest dose. Subsequently, 13 patients with osteosarcoma and one with metastatic paraganglioma have been treated at 30 mCi/kg.

^{153}Sm-EDTMP (Quadramet; samarium lexidronam) was obtained from Cytogen (Dupont Pharma Radiopharmaceuticals; Berlex Laboratories, Boston, MA). Because of short physical half-life (47 hours), ^{153}Sm-EDTMP was usually ordered 1 to 2 weeks before use, shipped on a Tuesday, and treatment preferentially given on Wednesday. ^{153}Sm-EDTMP was given intravenously (IV) through a central line into an IV containing normal saline over 10 minutes at doses of 6 mCi or less and over 30 minutes for higher doses using a shielded syringe pump and low-volume pediatric connection tubing. Calcium gluconate 10% (0.75 mL/10kg) was available for treatment of symptomatic hypocalcemia, if needed. Patients were given IV fluids two times as maintenance, before and 18 to 24 hours after ^{153}Sm-EDTMP, and instructed to void frequently for the first 8 hours after the infusion. Initial ^{153}Sm-EDTMP infusions and 48 hours of monitoring of blood and urine radioactivity were performed at the Mayo Clinic General Clinical Research Unit; subsequent patients have been treated on a hospital clinical unit familiar with handling of radioisotopes.

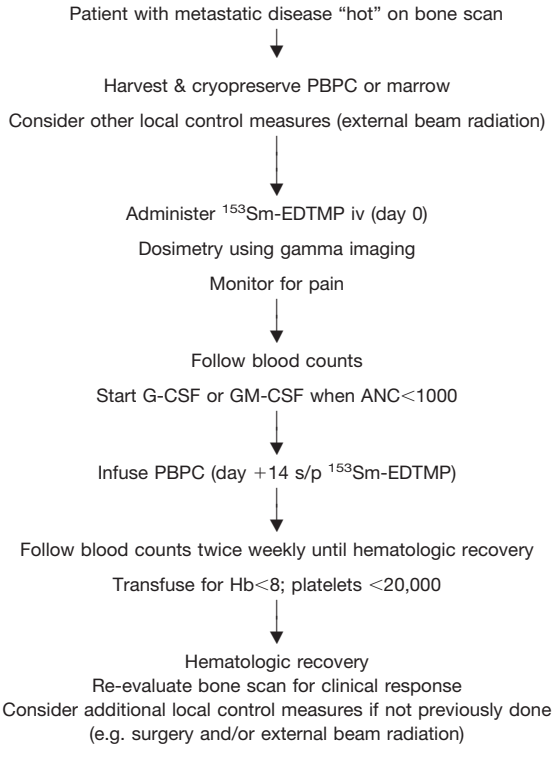

Fig 1. Treatment schema for high-dose ^{153}Sm-EDTMP with PBPC or marrow support.

Bone scans with copper attenuation shielding were used to determine distribution and dosimetry of the radioisotope at 2, 4, 24, and 48 hours in initial cohorts. Dosimetry at the MTD (30 mCi/kg) was done on day +1, +2, and +5 to determine estimated dose to indicator lesion, as well as whole-body radioactivity estimate. The latter was used to determine when natural decay to a total of less than 3.6 mCi, the safe upper limit for PBPC or marrow infusion, would occur.

Follow-Up Evaluations

Patients were instructed to expect neutropenia and need for RBC transfusions if the hemoglobin level reached less than 8 g/dL, platelet transfusions if platelets reached less than 20,000/μL, and to begin treatment with granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor if the absolute neutrophil count (ANC) reached less than 1,000/μL. All patients received PBPCs or marrow on day +14. Clinical response was assessed by bone scan and routine imaging techniques (magnetic resonance imaging or computed tomography). To qualify for follow-up scan evaluation, hematologic recovery was required. Follow-up evaluation also included pulmonary function testing, creatinine clearance, complete blood cell count, and quantitative bone scan with assessment of intensity of indicator lesion. The latter involves obtaining a standard bone scan at 4 hours and 24 hours, at which time only osseous distribution of tracer remains (ie, 100% bound to bone or bone-forming tumor). Follow-up scan was compared with a pretherapy quantitative bone scan.

RESULTS

Patient Characteristics

Clinical characteristics of the 27 patients with bone lesions treated with ^{153}Sm-EDTMP are summarized in Table 1. Twenty-one of 27 had osteosarcoma. All patients had two or more prior therapies and multiple sites of bone disease. Despite bone metastases, performance status was good or excellent in 24 of 30 patients. In general this was a group of young patients; the mean and median ages were 24.0 and 18 years, respectively. The oldest patient treated was 57 years of age. Because of concern about growth plate uptake, radioisotope treatment was offered to only two patients younger than 12 years; both patients had extensive disease and need for severe pain palliation. Four of four patients with an Eastern Cooperative Oncology Group performance status of 2 had numerous lung metastases in addition to bone metastases. PBPC mobilization using

G-CSF was generally well tolerated by most patients, with only two of 12 patients in the first three cohorts experiencing increased bone pain and opiate requirements for 1 to 3 days during mobilization.

A variety of chemotherapy schedules were sometimes used before cytokine mobilization for patients receiving doses greater than 6 mCi/kg. These included cyclophosphamide 2 g/m^2/d, etoposide 500 mg/m^2/d times three, ifosfamide/mesna 1,800 mg/m^2/d plus etoposide 100 mg/m^2/d for 5 days, and gemcitabine 2,100 mg/m^2/d on days 0 and 7. Nine of 13 osteosarcoma patients in the 30 mCi/kg cohort had PBPCs collected and infused on day +14 at the referring institution. These patients received samarium and dosimetry only at Mayo Clinic.

Immediate Toxicity and Adverse Effects

Immediate side effects during ^{153}Sm-EDTMP infusion were rare. Because high-dose ^{153}Sm-EDTMP could have clinically significant effects related to blood calcium chelation, subjects were asked whether they experienced any tingling of hands or fingers or oral numbness during or immediately after ^{153}Sm-EDTMP infusion. No symptoms suggestive of hypocalcemia were seen until 30 mCi/kg. The 30-minute ^{153}Sm-EDTMP infusion was not associated with other subjective or objective side effects, such as nausea or vomiting.

Radioactivity Biodistribution

Pretherapy ^{99m}Tc-MDP bone scans and gamma camera imaging after ^{153}Sm-EDTMP seemed to be nearly identical. In myeloma patients treated with 6 to 30 mCi/kg, binding of ^{153}Sm-EDTMP to bone surfaces was high.[13] At the highest dose used, 30 mCi/kg, estimates of between 92 and 420 Gy absorbed to bone surfaces were seen (Fig 2). Calculated or measured whole-body radioactivity and total dose of ^{153}Sm-EDTMP injected and residual whole-body radioactivity detected on day +13 is detailed in Table 2. At 30 mCi/kg of ^{153}Sm-EDTMP (ie, after 1,400 to 2,700 mCi of ^{153}Sm-EDTMP), residual measured radioactivity was variable but related to total dose administered. All patients were well within the safety limit of 3.6 mCi/kg for PBPC or marrow infusion on day +14. Figures 3 to 5 show representative radioisotope scans after ^{153}Sm-EDTMP infusion.

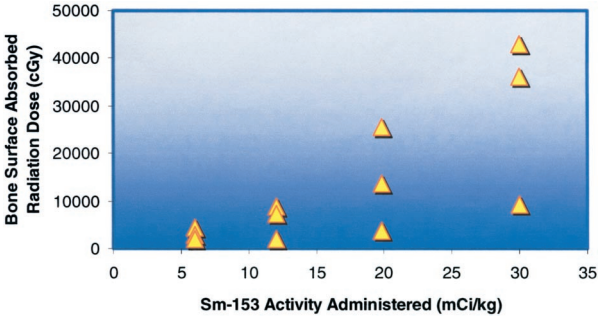

Fig 2. Relationship of ^{153}Sm-EDTMP dose and radioactivity absorbed to bone surfaces.

Table 2. Residual Whole-Body Radioactivity After High-Dose ^{153}Sm-EDTMP

^{153}Sm-EDTMP		Radioactivity on Day +13	
mCi/kg	Total (mCi)	Indicator Lesion(s)	mCi
3	151	Mediastinum	70
4.5	351	Spine, ribs	50
4.5	238	Spine	480
6	416	Spine	276
6	525	Humerus	616
6	558	Humerus, spine, tibia	791
12	386	Spine, lungs, ribs, femur	1,008
30	1,475	Marrow	1,069
30	1,500	Spine, shoulder	930
30	1,500	Maxilla	1,440
30	1,500	Humerus	1,850
30	1,500	Manubrium, shoulder	2,300
30	1,565	Spine	2,504
30	1,590	Tibia	2,100
30	1,890	Spine	1,270
30	2,190	Pelvis	1,830
30	2,700	Humerus	1,927

Delayed Toxicity and Adverse Effects

Four patients did not have marrow or PBPCs available and were provided with 1 mCi/kg of ^{153}Sm-EDTMP; mild to moderate self-limited pancytopenia lasting up to 5 weeks was seen. All high-dose ^{153}Sm-EDTMP patients experienced severe pancytopenia with grade 2 to 4 anemia, leukopenia, and thrombocytopenia. Some patients had transfusion of RBCs or platelets before PBPC or marrow infusion. After high-dose ^{153}Sm-EDTMP, 26 of 26 patients eventually required RBC and/or platelet transfusion support. To increase patient safety and reduce duration of hematologic toxicity, PBPC (n = 25) or marrow (n = 1) support was provided as per protocol. Autologous PBPCs or marrow was infused on day +14 after ^{153}Sm-EDTMP in all patients. Twenty-two of 25 patients were discharged within 6 hours of PBPC or marrow infusion.

Follow-up care after stem-cell infusion was performed on an outpatient basis. To minimize duration of neutropenia, high-dose ^{153}Sm-EDTMP patients received G-CSF or granulocyte-macrophage colony-stimulating factor within 10 to 16 days of ^{153}Sm-EDTMP infusion. Duration of cytokine administration ranged from 4 days to more than 4 weeks. All patients had recovery of ANC to more than 1,000/μL

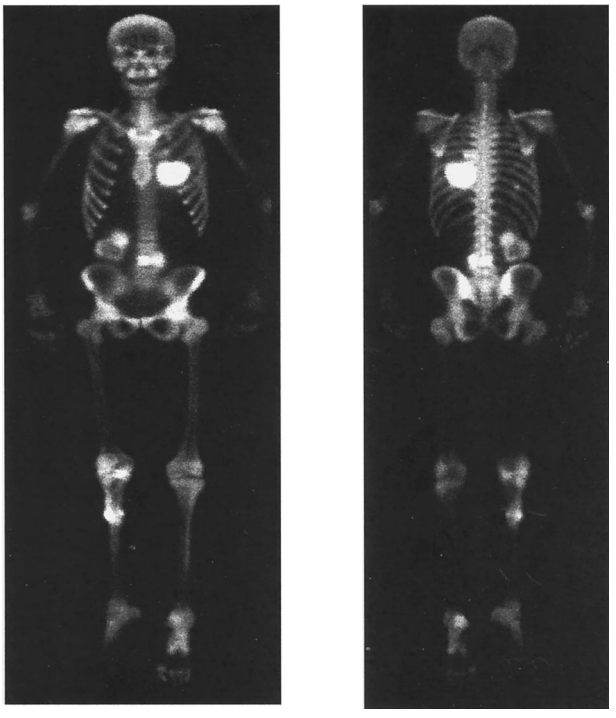

Fig 3. Variable uptake of ^{153}Sm-EDTMP in metastatic osteosarcoma: anterior and posterior gamma camera imaging 24 hours after administration of 3 mCi/kg. Note the more avid radioisotope uptake of the left chest mass adherent to the pericardium compared with the spine and right renal metastases.

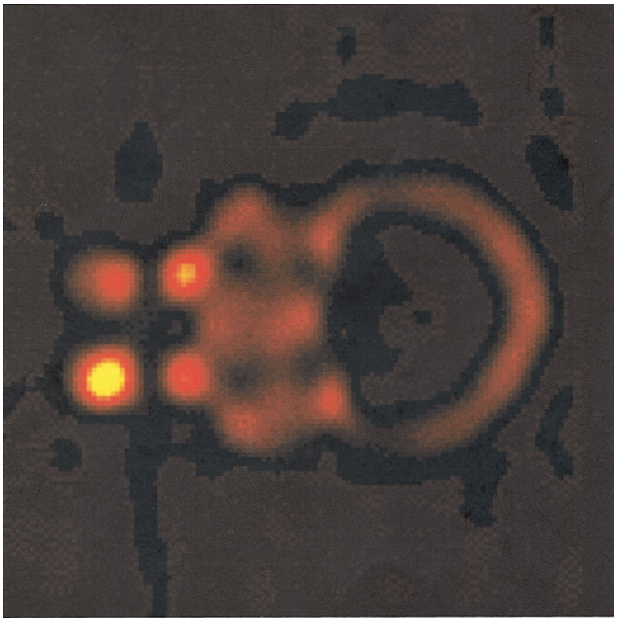

Fig 4. Bone-specific uptake including left mandible lesion after 6 mCi/kg of ^{153}Sm-EDTMP. Dosimetry indicated that the solitary osteoblastic lesion in the mandible received approximately 220 Gy. Single photon emission computed tomography imaging at 24 hours after ^{153}Sm-EDTMP administration.

within 2 to 3 weeks of PBPC infusion. Patients treated at 12, 19, and 30 mCi/kg had similar hematologic recovery, as long as the source of stem cells was adequate. The one patient treated at 30 mCi/kg who received marrow because of poor PBPC mobilization had slow neutrophil recovery (ANC $>$ 1,000/μL on day $+$26) and required 6 weeks to become platelet transfusion–independent. After receiving additional external-beam therapy, the platelet count is 20,000/μL (unsupported) 6 months after therapy. Another patient who received a graft containing 1.85×10^6 $CD34^+$/kg (collected over 8 days on two separate mobilization attempts) remains transfusion-dependent more than 4 months after 30 mCi/kg of ^{153}Sm-EDTMP but has had WBC recovery. Thus the 30 mCi/kg dose is myeloablative. Follow-up visits have demonstrated no significant effects on pulmonary function tests, renal function (serum creatinine or 24-hour creatinine clearance), or alkaline phosphatase isozymes levels after ^{153}Sm-EDTMP therapy.

Pain Palliation After ^{153}Sm-EDTMP

At the standard dose of 1 mg/kg, three of four patients had some improvement in pain. In patients treated with doses of 3 mCi/kg or more, 23 of 26 required opiates to control bone pain before ^{153}Sm-EDTMP. Many patients experienced increased bone pain for 12 to 48 hours after ^{153}Sm-EDTMP (flair reaction), then overall improvement. Most patients on opiates before high-dose ^{153}Sm-EDTMP were able to discontinue opiates within 2 to 4 weeks of receiving ^{153}Sm-EDTMP.

Imaging After ^{153}Sm-EDTMP

Gamma camera imaging (Figs 3 to 5) and dosimetry demonstrated specific and avid uptake of ^{153}Sm-EDTMP radioisotope in bone metastases and osteosarcoma lesions previously seen on bone scan. Pretreatment bone scan could predict fair, good, or excellent uptake of high-dose ^{153}Sm-EDTMP into indicator osteosarcoma lesions or bone metastases (Table 3). Figure 3 shows a representative patient from the 3.0 mCi/kg cohort. Some lesions had more intense uptake than others. Uptake of ^{153}Sm-EDTMP into indicator lesions has been variable, and dose estimates have ranged from 39 to 241 Gy (Table 3). Thus in some patients with avid bone scans, high-dose ^{153}Sm-EDTMP can deliver skeletal tumor irradiation with low nonhematologic toxicity.

DISCUSSION

Our study is the first report experience with very high-dose (30 mCi/kg) ^{153}Sm-EDTMP with PBPC support.

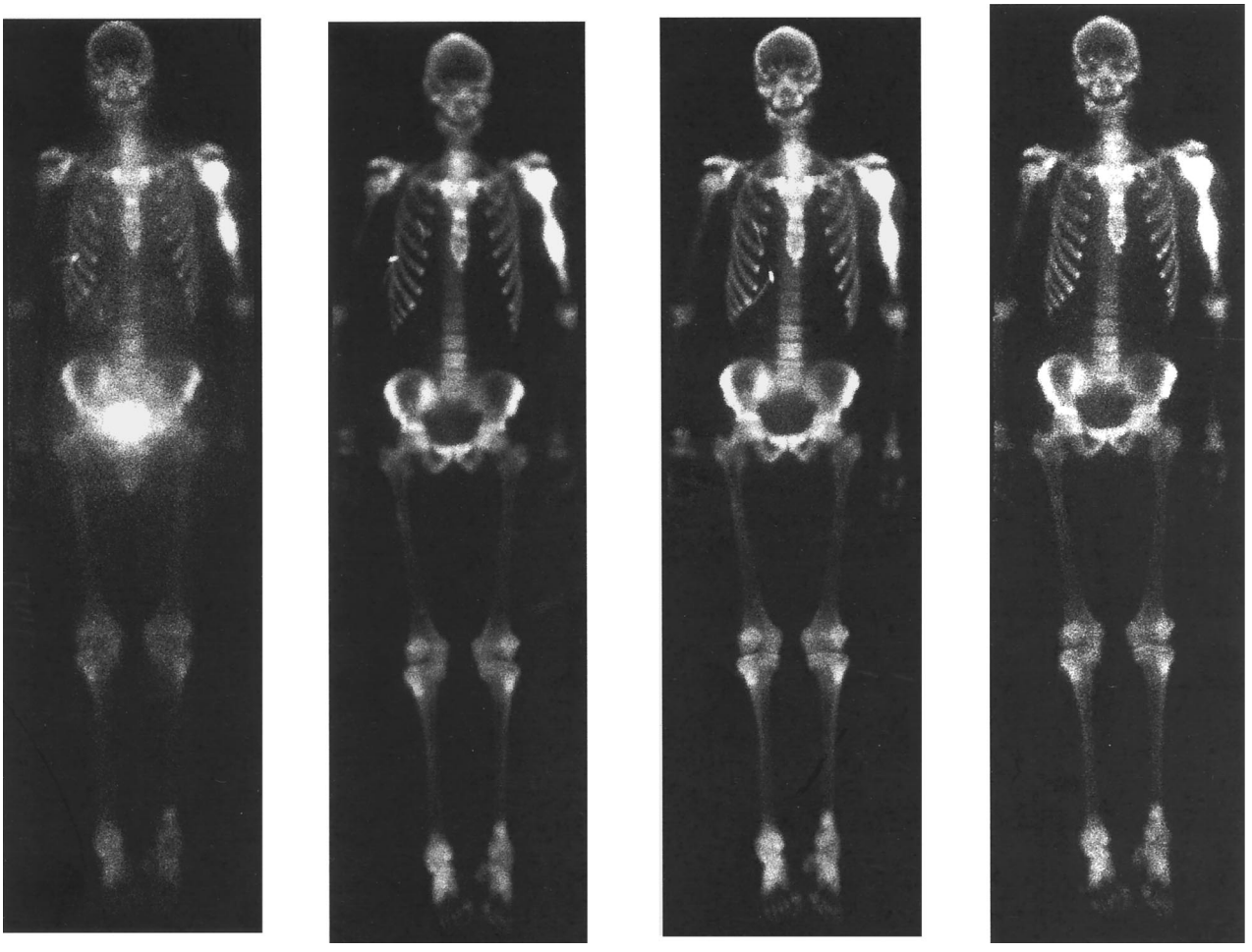

Fig 5. Whole-body gamma camera imaging of osteosarcoma of the left humerus and additional bone metastases (left rib, right sacroiliac joint, L5 spine) at 2, 24, 48, and 120 hours (right to left) after 6 mCi/kg of ^{153}Sm-EDTMP. The left humerus received an estimated 193 Gy.

Skeletal irradiation using this bone-seeking radioisotope had low nonhematologic toxicity and provided pain palliation for patients with osteosarcoma local recurrences or osteoblastic bone metastases. The key findings of the study were low nonhematologic toxicity and pain palliation.

Table 3. Radiation Dose Estimates to Osteosarcoma Lesions

^{153}Sm-EDTMP (mCi/kg)	Indicator Lesion	Radiation Dose (Gy)
3	Mediastinum	45
6	Mandible	220
6	Humerus	180
30	Maxilla	218
30	Manubrium	211
30	Skull	241
30	Femur	189
30	T6 spine	161
30	Humerus	39
30	L2, L3 spine	40

^{153}Sm-EDTMP is a radiopharmaceutical useful for palliation of bone pain.[3,14-28] Physical decay allowed PBPC to be safely given within 14 days of high-dose ^{153}Sm-EDTMP. Escalation beyond 30 mCi/kg may be possible if ^{153}Sm-EDTMP is infused more slowly or on different days. The only other bone-seeking isotope approved by the United States Food and Drug Administration, strontium-89 chloride, has a half-life that is too long (approximately 50 days) to permit dose escalation with PBPC support.

Except for mild, transient hypocalcemia at 30 mCi/kg and a possibly higher incidence of initial flair of bone pain, high-dose ^{153}Sm-EDTMP was not associated with nonhematologic side effects. Overall palliation of pain was impressive, with patients eventually requiring either

less opiate medication or being able to discontinue opiates. Quality of life was excellent and outpatient status was maintained.

The major toxicity of high-dose ^{153}Sm-EDTMP is hematologic. This is due to the proximity of red marrow and the beta-emitting radioisotope localized to bone surfaces. The dose of ^{153}Sm-EDTMP reached in our study was 30-fold more than the standard palliative ^{153}Sm-EDTMP dose. To our knowledge, this is the highest dose escalation achieved to date for any agent accompanied with stem-cell support. Dosimetry indicates that radiation dose to red marrow at 30 mCi/kg may be myeloablative; this was experienced in the two patients receiving marginal doses of hematopoietic stem cells. The combination of melphalan and ^{153}Sm-EDTMP was found to be myeloablative in preclinical[29,30] and clinical[13] studies, whereas ^{153}Sm-EDTMP or melphalan alone resulted in self-limiting myelosuppression. Thus use of a bone-seeking radioisotope in combination with chemotherapy may be synergistic on marrow micrometastases and osteoblastic bone metastases.[31,32]

Osteosarcoma patients treated with palliative doses of ^{153}Sm-EDTMP have been previously reported.[11,12] Thus osteosarcoma is an attractive target for the combination of external-beam radiotherapy and ^{153}Sm-EDTMP.[12,33] In view of the minimal toxicity of ^{153}Sm-EDTMP in our study and the apparent dose response of ^{153}Sm-EDTMP alone on tumor-free survival in an orthotopic human osteosarcoma model,[34] high-dose ^{153}Sm-EDTMP with PBPC support is worthy of further investigation.

ACKNOWLEDGMENT

We thank Cynthia Miller for expert secretarial assistance; the Mayo Clinic General Clinical Research Center (GCRG), nurses on station 72 at Rochester Methodist Hospital, and Mayo Eugenio Litta Children's Hospital for the extra efforts; and Shelly Rank for compassionate and comprehensive radioisotope scanning. Detailed data monitoring by Sharon Bell, helpful discussions with John Edmonson and Charles Erlichman in the Mayo Clinic Department of Oncology, and protocol development and administration by the Mayo Cancer Center are also acknowledged.

REFERENCES

1. Mausner LF, Kolsky KL, Joshi V, et al: Radionuclide development at BNL for nuclear medicine therapy. Appl Radiat Isot 4:285-294, 1998

2. Goeckeler WF, Troutner DE, Volkert WA, et al: 153 Sm radiotherapeutic bone agents. Nucl Med Biol 13:479-482, 1986

3. Goeckeler WF, Edwards B, Volkert WA, et al: Skeletal localization of Samarium-153 chelates: Potential therapeutic bone agents. J Nucl Med 28:495-504, 1987

4. Laznicek M, Laznickova A, Budsky F, et al: Comparison of biological characteristics of EDTMP complexes with ^{99m}Tc, ^{111}In and ^{153}Sm in rats. Appl Radiat Isot 45:949-953, 1994

5. Lattimer JC, Corwin Jr LA, Stapleton J, et al: Clinical and clinicopathologic response of canine bone tumor patients to treatment with samarium 153 EDTMP. J Nucl Med 31:1316-1325, 1990

6. Aas M, Moe L, Gamlem H, et al: Internal radionuclide therapy of primary osteosarcoma in dogs using 153Sm-ethylene-diamino-tetramethylene-phosphonate (EDTMP). Clin Cancer Res 5:3148s-3152s, 1999 (suppl)

7. Lattimer JC, Corwin Jr LA, Stapleton J, et al: Clinical and clinicopathologic effects of ^{153}EDTMP administered intravenously to normal beagle dogs. J Nucl Med 31:586-593, 1990

8. Appelbaum FR, Sandmaier B, Brown PA, et al: Myelosuppression and mechanism of recovery following administration of 153 Samarium-EDTMP: Antibody Imunoconjug Radiopharmaceuticals 1:263-270, 1988

9. Turner JH, Claringbold PG, Heytherington EL: A phase I study of samarium 153 ethylene diamine tetramethylene phosphonate therapy for disseminated skeletal metastases. J Clin Oncol 7:1926-1931, 1989

10. Turner JH, Martindale AA, Sorby P: Samarium ^{153}EDTMP therapy of disseminated skeletal metastasis. Eur J Nucl Med 15:784-795, 1989

11. Bruland OS, Skretting A, Solheim OP, et al: Targeted radiotherapy of osteosarcoma using 153Sm-EDTMP. Acta Oncologica 35:381-384, 1996

12. Bruland OS, Skretting A, Solheim OP, et al: Targeted radiotherapy of osteosarcoma using 153 Sm-EDTMP: A new promising approach. Acta Oncol 35:381-384, 1996

13. Dispenzieri A, Wiseman GA, Lacy MQ, et al: A phase I study of a conditioning regimen for peripheral blood stem cell transplantation for multiple myeloma: 153-samarium ethylene diamine tetramethylene diphosphonate (153-Sm-EDTMP) and melphalan. Blood 95:588a, 2000 (abstr)

14. Turner JH, Claringbold PG, Hetherington EL, et al: A phase I study of ^{153}Samarium ethylene diamine tetramethylene phosphonate for disseminated skeletal metastases. J Clin Oncol 7:1926-1931, 1989

15. Sandeman TF, Budd RS, Martin JJ: Samarium 153 labeled EDTMP: for bone metastases from cancer of the prostate. Clin Oncol 4:160-164, 1992

16. Holmes RA: ^{153}Sm EDTMP: A potential therapy for bone cancer pain. Semin Nucl Med 22:41-45, 1992

17. Collins C, Eary JF, Donaldson G, et al: Samarium ^{153}EDTMP in bone metastases of hormone refractory prostate carcinoma: A phase I/II trial. J Nucl Med 34:1839-1844, 1993

18. Resche I, Chatal JF, Pecking A, et al: A dose-controlled study of ^{153}Sm-ethylenediaminetetramethylene phosphonate (EDTMP) in the treatment of patients with painful bone metastases. Eur J Can 33:1583-1591, 1997

19. Serafini AN, Houston SJ, Resche I, et al: Palliation of pain associated with metastatic bone cancer using samarium 153 Lexidronam: A double-blind placebo-controlled clinical trial. J Clin Oncol 16:1574-1581, 1998

20. Tian J, Zhang J, Hou Q, et al: Multicentre trial on the efficacy and toxicity of single-dose samarium 153 ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. Eur J Nucl Med 26:2-7, 1999

21. Alberts AS, Smit BJ, Louw KA, et al: Dose response relationship and multiple dose efficacy and toxicity of samarium 153-EDTMP in metastatic cancer to bone. Radiother Oncol 43:175-179, 1997

22. Louw WKA, Dormehl IC, van Rensburg AJ, et al: Evaluation of samarium 153 and holmium 166 EDTMP in the normal baboon model. Nucl Med Biol 23:935-940, 1996

23. Ketring AR: ^{153}Sm-EDTMP and ^{186}Re-HEDP as bone therapeutic radiopharmaceuticals. Nucl Med Biol 14:223-232, 1987

24. Shibamoto Y, Horii N, Takahashi M: Long-term control of multiple lung metastases from osteosarcoma obtained by conventional radiotherapy: A case report. Oncol Rep 6:1085-1087, 1999

25. Singh A, Holmes RA, Farhangi M, et al: Human pharmacokinetics of samarium 153 EDTMP in metastatic cancer. J Nucl Med 30:1814-1818, 1989

26. Heggie JC: Radiation absorbed dose calculations for samarium ^{153}EDTMP localized in bone. J Nucl Med 32:840-844, 1991

27. Eary JF, Collins C, Stabin M, et al: Samarium 153 EDTMP biodistribution and dosimetry estimation. J Nucl Med 34:1031-1036, 1993

28. Bayouth JE, Macey DJ, Kasi LP, et al: Dosimetry and toxicity of samarium ^{153}EDTMP administered for bone pain due to skeletal metastases. J Nucl Med 35:63-69, 1994

29. Turner JH, Claringbold PG, Berger JD, et al: 153Sm-EDTMP and melphalan chemo-radiotherapy regimen for bone marrow ablation prior to marrow transplantation: An experimental model in the rat. Nucl Med Commun 13:321-329, 1992

30. Turner JH, Claringbold PG, Manning LS, et al: Radiopharmaceutical therapy of 5T33 murine myeloma by sequential treatment with samarium 153 ethylene diamine tetramethylene phosphonate, melphalan, and bone marrow transplant. J Natl Cancer Inst 85:1508-1513, 1993

31. Porter AT, Ben-Josef E, Davis L: Systemic administration of new therapeutic radioisotopes, including phosphorus, strontium, samarium, and rhenium. Curr Opin Oncol 5:607-610, 1994

32. Ben-Josef E, Porter AT: Radioisotopes in the treatment of bone metastases. Ann Med 29:31-35, 1997

33. Bruland OS, Phil A: On the current management of osteosarcoma: A critical evaluation and proposal for a modified treatment strategy. Eur J Cancer 33:1725-1731, 1997

34. Winderen M, Kjonniksen I, Fodstat O: Pronounced therapeutic effect of samarium 153 ethylenediaminetetramethylene phosphonate in an orthotopic human osteosarcoma tibial tumor model. J Natl Cancer Inst 87:221-222, 1995