# Gemcitabine Radiosensitization after High-Dose Samarium for Osteoblastic Osteosarcoma

Peter M. Anderson,[1] Gregory A. Wiseman,[2] Linda Erlandson,[2] Vilmarie Rodriguez,[2] Barbara Trotz,[2] Stephen A. Dubansky,[3] and Karen Albritton[4]

**Abstract** Osteoblastic metastases and osteosarcoma can avidly concentrate bone-seeking radiopharmaceuticals. We sought to increase effectiveness of high-dose $^{153}$Samarium ethylenediaminetetramethylenephosphonate ($^{153}$Sm-EDTMP, Quadramet) on osteosarcomas using a radiosensitizer, gemcitabine. Fourteen patients with osteoblastic lesions were treated with 30 mCi/kg $^{153}$Sm-EDTMP. Gemcitabine was administered 1 day after samarium infusion. Residual total body radioactivity was within the safe range of <3.6 mCi on day +14 (1.1 $\pm$ 0.4 mCi; range, 0.67-1.8 mCi). All patients received autologous stem cell reinfusion 2 weeks after $^{153}$Sm to correct expected grade 4 hematopoietic toxicity. Peripheral blood progenitor cells were infused in 11 patients; three patients had marrow infused. Blood count recovery was uneventful after peripheral blood progenitor cells in 11 of 11 patients. Toxicity from a single infusion of gemcitabine (1,500 mg/m$^2$) in combination with $^{153}$Sm-EDTMP was minimal (pancytopenia). However, toxicity from a daily gemcitabine regimen (250 mg/m$^2$/d $\times$ 4-5 days) was excessive (grade 3 mucositis) in one of two patients. There were no reported episodes of hemorrhagic cystitis (hematuria) or nephrotoxicity. At the 6- to 8-week follow-up, there were six partial remissions, two mixed responses, and six patients with progressive disease. In the 12 patients followed >1 year, there have been no durable responses. Thus, although high-dose $^{153}$Sm-EDTMP + gemcitabine has moderate palliative activity (improved pain; radiologic responses) in this poor-risk population, additional measures of local and systemic control are required for durable control of relapsed osteosarcoma with osteoblastic lesions. The strategy of radioactive drug binding to a target followed by a radiosensitizer may provide synergy and improved response rate.

Although bone metastases of primary bone tumors herald a very poor prognosis (1, 2), radiotherapy can be help control disease and reduce pain (3, 4). There has been little improvement in results of osteosarcoma chemotherapy protocols in the past decade; most programs achieve 55% to 70% survival in nonmetastatic extremity tumors (5–7). There is a need for improved control for patients with osteosarcoma in axial sites (40-60% control; refs. 8–10), metastases (20-30% durable control; ref. 2), or recurrent disease (10-20% control; ref. 11). With modern therapy, about 20% of relapses occur in bone (12).

$^{153}$Samarium ethylenediaminetetramethylenephosphonate ($^{153}$Sm-EDTMP) is a bone-seeking radiopharmaceutical (Table 1) designed to selectively deliver radiation to osteoblastic skeletal metastases (13–18). Use of $^{153}$Sm-EDTMP has been described in canine (19, 20) and human osteosarcoma (21–24). Although the dose-limiting toxicity of $^{153}$Sm-EDTMP is pancytopenia related to radiation of bone marrow, the relatively short half-life of this $\beta$-emitting radioisotope (47 hours) has permitted a 30-fold dose increase if stem cell support is provided 2 weeks after administration (22, 23).

One means to improve the therapeutic index of radiotherapy against sarcomas is the use of a radiosensitizer (25). Gemcitabine is a nucleoside analogue with activity against solid tumors (26–28) and is a radiation sensitizer (29–34). Because $^{153}$Sm-EDTMP has very little washout after skeletal localization (35, 36), gemcitabine after $^{153}$Sm-EDTMP should facilitate improved radiobiological effectiveness against cancer cells in the immediate vicinity of the radioisotope. In this report, we sought to determine toxicity and effects of targeted skeletal radiation using gemcitabine after $^{153}$Sm-EDTMP in patients with osteosarcoma.

## Materials and Methods

Patients with metastatic, unresectable, progressive, and/or recurrent osteosarcoma involving bone were eligible for treatment and accrued during 2001 to 2003 if:

1. state-of-the art chemotherapy (e.g., two or more regimens) had been given,
2. at least one osteoblastic indicator lesion was observable on $^{99m}$Tc-MDP bone scan (qualitative, yes/no increase in osteoblastic activity compared with contralateral side)

**Authors' Affiliations:** [1]M.D. Anderson Cancer Center, Houston, Texas; [2]Mayo Clinic, Rochester, Minnesota; [3]State University of New York Upstate Medical University, Syracuse, New York; and [4]Dana-Farber Cancer Institute, Boston, Massachusetts

Received 3/21/05; revised 5/25/05; accepted 7/7/05.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Requests for reprints:** Peter M. Anderson, Pediatrics, Unit 87, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009. Phone: 713-563-0893; Fax: 713-794-5042; E-mail: pmanders@mdanderson.org.



doi:10.1158/1078-0432.CCR-05-0628

**Table 1.** Properties and characteristics of $^{153}$Sm-EDTMP (Quadramet)

| Characteristic | Property |
|---|---|
| Skeletal targeting | Metabolized into bone and osteoblastic bone metastases |
| Bone seeking | Bone/liver ratio = 700 |
| Radioactivity | |
| γ (103 keV) | 0.29 (suitable for imaging) |
| β (640 keV) | 0.3 emissions/disintegration |
| β (710 keV) | 0.5 emissions/disintegration |
| β (810 keV) | 0.2 emissions/disintegration |
| Average β particle | 223 keV |
| Penetration | ~1 mm |
| Half-life | 47 h |
| Source and synthesis | Neutron irradiation of $^{152}$Sm, then EDTMP chelation |
| Molecular weight | 696 |
| Dose | |
| standard | 1 mCi/kg; 37 MBq/kg |
| high-dose | 6-30 mCi/kg; 500-3,000 mCi total; ~15-60 mL in the United States; 222-1,100 MBq/kg |
| Specific activity | 20-46 mcg/mL |
| Organ distribution | Bone ›› marrow › bladder wall › kidney › liver = spleen = lung |
| Time of radioactive decay to level, safe for hematopoietic stem cell infusion | 9-13 d after high-dose $^{153}$Sm-EDTMP (6-30 mCi/kg) Total body radioactivity is ‹3.6 mCi |

3. other therapies of higher priority for local control (e.g., surgery or radiotherapy) were either not possible or refused
4. age was ≥12 years and adolescents had achieved growth potential or were willing to accept linear growth delay from radiation to growth plates.

Autologous hematopoietic stem cells were cryopreserved. Informed consent was obtained in all patients after consultation including discussion of indications, risks, and alternatives. Patient characteristics and indicator lesion(s) are in Table 2. Stem cells were harvested using a variety of chemotherapy regimens followed by granulocyte colony-stimulating factor. All patients had central lines for $^{153}$Sm-EDTMP infusion, hydration, stem cell infusion, blood count monitoring, and transfusions.

$^{153}$Sm-EDTMP (Quadramet, Cytogen, Princeton, NJ) infusions were scheduled on Wednesdays; thus, the high-dose infusion would have the highest specific activity. To decrease risk of symptomatic hypocalcemia, 1,000-mg calcium carbonate was given orally every hour for 3 hours before the $^{153}$Sm-EDTMP infusion. Calcium gluconate (10%; 7.5 mg/kg in 50 mL D5W) was available for treatment of hypocalcemia but was not needed in any patient.

***Samarium administration.*** Hydration consisted of D5 and 0.45% NaCl with KCl 20 meq/L at 125 mL/m$^2$/h for 3 hours. $^{153}$Sm-EDTMP was thawed and placed into a 60-mL lead-shielded plastic syringe. $^{153}$Sm-EDTMP (30 mCi/kg; 1,110 MBq/kg) was infused i.v. via a central line using small bore pediatric tubing to minimize the amount remaining in the tubing that was flushed into the patient at the end of the infusion using 10 mL of 0.9% NaCl. Furosemide (0.5 mg/kg i.v.) was then given. Instructions to empty the bladder frequently (e.g., q 1-2 hours × 6 hours) were given and i.v. hydration was continued for about 20 hours after the samarium infusion.

***Gemcitabine administration.*** Antiemetic therapy consisted of granisetron (1 mg orally) and dexamethasone (8 mg orally). Gemcitabine (Gemzar; Lilly, Indianapolis, IN; 250 mg/m$^2$/dose in the first two patients using daily × 2, rest day, then daily × 2 patient 1; daily × 5 patient 2 and 1,500 mg/m$^2$ in the subsequent 12 patients) was diluted in 500 mL of 0.9% NaCl and administered i.v. over 30 minutes. Chemotherapy was done as an outpatient. Gemcitabine schedule was initially repetitive daily dosing with daily × 2, day of rest, then daily × 2 (patient 1; patient choice not to get dose 3 of 5), then daily × 5 (patient 2). When this patient developed unexpected grade 4 mucositis, the schedule the single dose schedule 18 to 24 hours after was used (patients 3-14).

Whole body radioactivity was measured at three time points (usually day +1, +2, and +5; e.g., Thursday, Friday, and Monday after samarium). Residual radioactivity was estimated for day 14 after $^{153}$Sm-EDTMP to confirm that total body radiation was <3.6 mCi, the safe upper limit for stem cell infusion. Autologous stem cells were thawed and infused 2 weeks s/p $^{153}$Sm-EDTMP according to standard clinical guidelines. Patients received routine supportive care including red cell and platelet transfusions. Levofloxicin (500 mg) orally daily and either granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor was given s.c. daily after stem cells until neutrophil recovery.

***Imaging and follow-up studies.*** Bone scans and in selected cases, chest computerized tomography and positron emission tomography scans were done. Serum alkaline phosphatase and creatinine were monitored. Imaging responses were defined as complete remission: the disappearance of lesion(s) on bone scan or positron emission tomography scan; partial remission: persistence but improvement on bone and/or positron emission tomography; stable: no change; and progression: appearance of new lesions or >25% increase in size of an indicator lesion measured using computerized tomography scan. Because patients were accrued 2001 to 2003, follow-up was available on all patients for at least 1 to 2 years.

## Results

***High-dose samarium and radioactive decay.*** A total of 14 patients received high-dose $^{153}$Sm-EDTMP and gemcitabine as described in Tables 2 and 3. Using 30 mCi/kg actual weight calculation, an average of 1,640 mCi $^{153}$Sm-EDTMP was administered. The residual radioactivity before stem cell infusion (i.e., 14 days after high-dose $^{153}$Sm-EDTMP) was about 1 mCi (range, 0.67-1.8; Table 4). This amount was within the safe limit of <3.6 mCi for stem cell infusion.

***Performance.*** The treatment group had variable performance status before treatment (Table 2). After treatment, all patients maintained stable or improved performance status except the single patient with poor initial performance status of 2. This patient had some alleviation of pain but did not improve enough to have outpatient pain management.

***Toxicity.*** Neither nephrotoxicity nor hemorrhagic cystitis was a problem. Serum creatinine did not change nor was hematuria seen. As expected, all patients had temporary cytopenias. All patients required transfusions and were supported with granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor. The most serious toxicity was life-threatening pulmonary hemorrhage in a patient with multiple (>50), small lung metastases in addition to indicator bone lesion in the tibia. This occurred during severe thrombocytopenia (platelets < 10,000). Hemorrhage resolved with supportive care including transfusions and

**Table 2.** Osteosarcoma patients with lesion(s) for which surgical control was not possible treated with high-dose $^{153}$Sm-EDTMP + gemcitabine

| Age/PS | Number of prior | | |
|---|---|---|---|
| | Chemotherapy regimens | Indicator lesion(s)-type/location | |
| 17/1 | 2 (std*, I/E†) | Metastatic | pleural metastases (4) |
| 16/1 | 3 (std, I/E, gem‡) | Metastatic | Frontal, left femur, lung |
| 20/0 | 3 (std, I/E,T/C§) | Metastatic | Spine (3) |
| 17/2 | 3 (std, I/E, gem) | Metastatic | R hilar (lung) |
| 18/0 | 2 (std, I/E) | Metastatic | R pelvis, lungs |
| 24/1 | 4 (std, ifos/dox, HDMTX, gem) | Metastatic | R tibia, lungs |
| 14/1 | 3 (std, I/E, other) | Secondary | R zygoma |
| 17/0 | 2 (std, I/E) | Metastatic | R tibia, lung |
| 16/1 | 4 (std, I/E, aGM-CSF‖, gem) | Metastatic | Spine |
| 20/0 | 2 (std, I/E) | Unresectable | R pelvis |
| 12/1 | 2 (std, I/E) | Secondary | L palate/maxilla |
| 20/1 | 2 (std, ICE¶) | Recurrent | Spine |
| 14/0 | 2 (std, I/E) | Secondary | Clivus |
| 13/1 | 3 (std, I/E, cyclophosphamide/E) | Metastatic | L pericardial/lingula |

Abbreviations: PS, performance status; GM-CSF, granulocyte macrophage colony-stimulating factor; dox, doxorubicin; ifos, ifosfamide; gem, gemcitabine.
*Std: *cis*-platinum + doxorubicin, high-dose methotrexate.
† Ifosfamide/mesna and etoposide.
‡ Gemcitabine.
§Tototecan and cyclophosphamide.
‖Aerosol GM-CSF.
¶Ifosfamide/carboplatin/etoposide.

administration of one dose (5.8 mg) of factor VIIa i.v. Mucositis was related to gemcitabine schedule and occurred only in the patient that was given low dose gemcitabine daily × 5. This patient also had poor oral intake from headache related to brain edema associated with a skull metastasis adjacent to the frontal lobe. No mucositis was seen after a much larger single dose of gemcitabine 1 day after samarium infusion. Five of 14 patients had fever when neutropenic. No patient with performance status of 0 had fever, but 50% (four of eight) patients with performance status of 1 had fever.

**Table 3.** Samarium + gemcitabine + stem cell doses

| Patient | $^{153}$Sm-EDTMP (total mCi) | Gemcitabine, dose (mg/m$^2$) | Stem cell (PBPC), CD34$^+$ × 10$^6$/kg |
|---|---|---|---|
| 1 | 1,500 | 250 × 4 of 5 d | 5.3 |
| 2 | 1,500 | 250 daily × 5 | 6.5 |
| 3 | 1,780 | 1,500 × 1 | 7.0 |
| 4 | 2400 | 1,500 × 1 | 5.7 |
| 5 | 1,500 | 1,500 × 1 | 5.3 |
| 6 | 1,980 | 1,500 × 1 | 2.8 |
| 7 | 1,260 | 1,500 × 1 | Marrow 1 × 10$^8$ nuc/kg |
| 8 | 1,900 | 1,500 × 1 | Marrow 4.1 × 0$^8$ nuc/kg |
| 9 | 1,960 | 1,500 × 1 | Marrow 5.6 × 10$^8$ nuc/kg |
| 10 | 1,200 | 1,500 × 1 | 6.0 |
| 11 | 1,080 | 1,500 × 1 | 1.8 |
| 12 | 1,880 | 1,500 × 1 | 5.4 |
| 13 | 1,275 | 1,500 × 1 | 3.0 |
| 14 | 1,840 | 1,500 × 1 | 2.0 |
| Median | 1,640 | | 5.3 |
| Mean | 1,647 | | 4.6 |
| SD | 376 | | 1.9 |
| SE | 100 | | 0.6 |

Abbreviation: PBPC, peripheral blood progenitor cell.

Although temporary lymphopenia was observed, there were no fungal or unusual opportunistic infections.

*Stem cell grafts.* In this very heavily pretreated cohort, 11 of 14 patients had successful peripheral blood stem cell harvesting and infusion (Table 3). In one of the three patients that had bone marrow harvested, delayed engraftment occurred. This patient also had the lowest number of nucleated marrow cells ($1 \times 10^8$/kg) infused. Recovery of leukocytes occurred within 3 weeks of peripheral blood progenitor cell infusion in all patients. Platelet recovery was more variable and as expected was longer in those that had marrow grafts.

*Response and quality of life.* Alkaline phosphatase decreased in six of eight patients in which both pre-therapy and post-therapy values were available (Table 5). Flair reaction requiring opiates for pain was uncommon (1 of 14). Indicator lesions were improved on imaging in 8 of 14. In the 12 patients with follow-up of >1 year, the longest duration of response was 11 months. Pattern of failure was progression at site of previous disease in 11 of 14 and development of new or worse pulmonary metastases in 3 of 14. Figure 1 shows representative imaging of osteoblastic tumors treated with $^{153}$Sm-EDTMP + gemcitabine. Early and rapid improvement in bone scan uptake were seen in some patients.

**Table 5.** Alkaline phosphatase and indicator lesion before versus after high-dose Samarium + gemcitabine

| | Alkaline phosphatase (units/L) | | Response of | |
|---|---|---|---|---|
| Patient | Pre | Post | Indicator lesion(s) | Pattern of failure |
| 1 | 506 | 348 | Mixed | Pleural |
| 2 | 1,739 | 765 | Mixed | Lung |
| 3 | 1,170 | NA | PR | Spine |
| 4 | NA | 2,616 | Progression | Lung |
| 5 | 221 | NA | PR | Lung, new spine |
| 6 | 331 | NA | Progression | Lung |
| 7 | 555 | 586 | Progression | Zygoma |
| 8 | 660 | 306 | Progression | R tibia |
| 9 | 260 | 230 | Progression | Spine |
| 10 | 212 | NA | PR | R ishium |
| 11 | NA | NA | PR | Palate/sinus |
| 12 | 271 | 352 | Progression | Spine |
| 13 | 307 | 59 | PR | Clivus |
| 14 | 2,922 | 158 | PR | Pericardial |

NOTE: Lung: new or worse pulmonary metastases. Failure at other sites: new lesion(s) or increase of existing osteoblastic indicator lesion.
Abbreviations: PR, partial remission; NA, not available.

## Discussion

Osteosarcoma is characterized by osteoid formation within the tumor. Effective therapy should involve local control with physical means (e.g., surgery and/or radiotherapy) as well as systemic therapy. Chemotherapy protocols have produced survival rates in the 55% to 70% range for nonmetastatic extremity osteosarcoma (37). Ifosfamide and etoposide have proven activity in metastatic osteosarcoma (1, 38). Efforts to increase the dose intensity of preoperative or high-risk disease have not improved results (11, 39, 40). This may be a function of innate insensitivity to chemotherapy (41).

Some newer chemotherapy agents have cytotoxic activity that is "non-cross-resistant." Aerosol gemcitabine has promising activity in murine osteosarcoma (42). Monoclonal antibodies with specificity against osteosarcoma are another option but have problems associated with heterogeneous targeting and nonspecific binding (43–45). The biology of osteosarcoma and potential targets of therapy has been recently reviewed (46).

Radiotherapy is considered only modestly effective in osteosarcoma and is generally used in situations when surgery is not possible or for pain (4). Radiotherapy had better than expected local control of extremity osteosarcoma in those that were also responding to chemotherapy (3). Previous experience using $^{153}$Sm-EDTMP for osteoblastic osteosarcoma has indicated that this bone-seeking radiopharmaceutical could be given at a very high dose to achieve significant radiation doses within tumors with minimal toxicity (23).

Radiosensitization with gemcitabine has been shown to occur *in vitro* and *in vivo* (32–34, 47, 48). Because $^{153}$Sm has a half-life of 47 hours, our initial attempt was to use a low daily dose (250 mg/m$^2$) of gemcitabine. Like an earlier report (49), a 5-day schedule of gemcitabine was toxic and associated with significant mucositis (>1 week); thus, the daily gemcitabine schedule was abandoned. However, a single 1,500 mg/m$^2$ gemcitabine dose after samarium had no immediate significant side effects.[5]

**Table 4.** Residual radioactivity on d +14 s/p high-dose $^{153}$Sm-EDTMP (30 mCi/kg)

| Patient | mCi |
|---|---|
| 1 | 0.76 |
| 2 | 1.10 |
| 3 | 1.01 |
| 4 | 1.34 |
| 5 | 0.57 |
| 6 | 1.04 |
| 7 | 1.48 |
| 8 | 1.80 |
| 9 | 1.02 |
| 10 | 0.67 |
| 11 | 1.18 |
| 12 | 1.77 |
| 13 | 0.71 |
| 14 | 0.71 |
| Median | 1.03 |
| Mean | 1.08 |
| SD | 0.40 |
| SE | 0.11 |

[5] Personal observations.

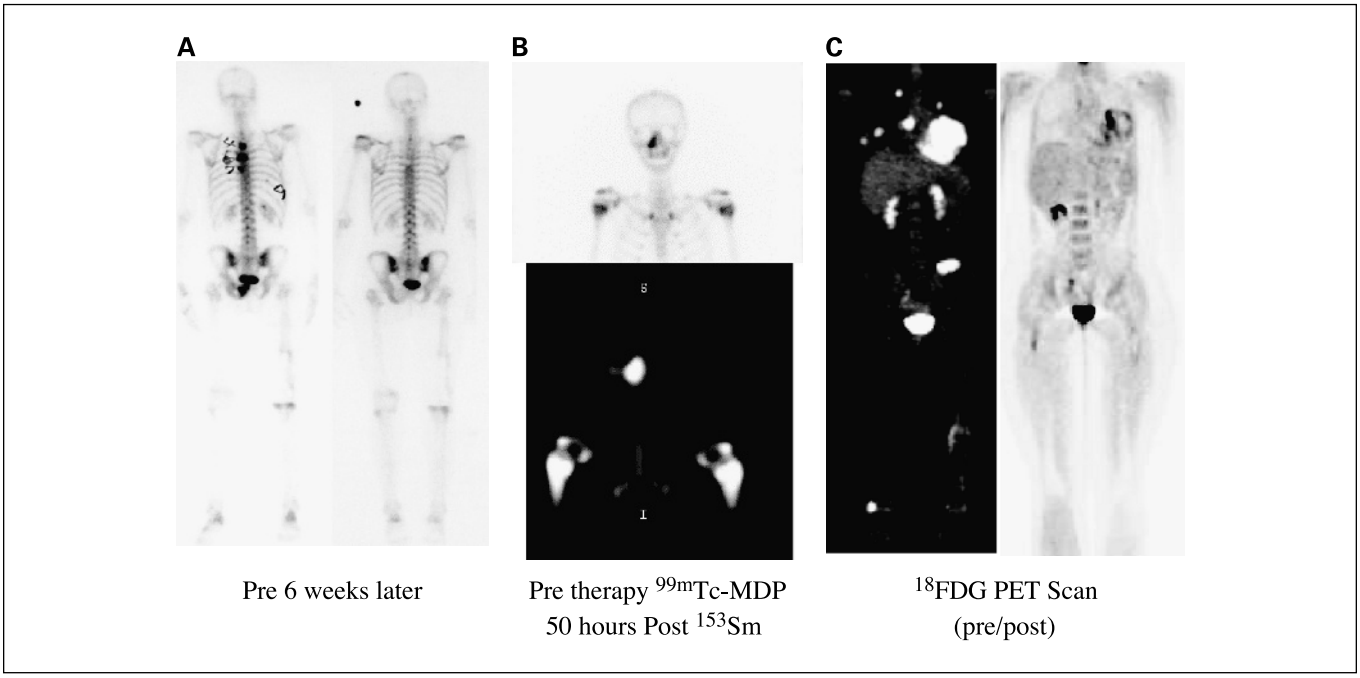


**Fig. 1.** *A*, osteoblastic metastases of the pelvis and spine before and after high-dose $^{153}$Sm-EDTMP and gemcitabine therapy. $^{99m}$Tc-MDP bone scan, posterior view. The lesion in the right ishium (just below isotope in the bladder) and the three spine metastases are no longer apparent after therapy. *B*, secondary osteosarcoma of the clivus before (*Pre*) and after (*Post*) high-dose $^{153}$Sm-EDTMP + gemcitabine therapy. *Top,* $^{99m}$Tc-MDP bone scan shows lesion at base of skull and symmetric, open epiphyseal plates in long bones. *Bottom,* imaging obtained 50 hours after infusion of $^{153}$Sm-EDTMP shows avid uptake in both the osteosarcoma skull lesion and growth plates. Note the almost identical deposition of $^{99m}$Tc-MDP and $^{153}$Sm-EDTMP into both growth plates and the osteoblastic tumor. *C*, metastatic osteosarcoma before and after $^{153}$Sm-EDTMP + gemcitabine therapy. Positron emission tomography (*PET*) scan showed improvement of numerous lesions 6 weeks after treatment.

$^{153}$Sm-EDTMP has very little washout after binding bone (35). Previous dosimetry measurements have shown organ/bone ratios with ~700-fold more $^{153}$Sm radioisotope deposited in bone compared with liver. This is in contrast to monoclonal antibodies in which organ/bone or bone marrow ratios are ~1 to 2. Thus, $^{153}$Sm-EDTMP is the most specific agent commercially available for targeting osteoblastic metastases of osteosarcoma. $^{223}$Radium is a newer bone-seeking radioisotope that has α emission and is being developed in Norway (50). Because $^{223}$Ra is relatively marrow sparing compared with $^{153}$Sm-EDTMP, this bone-seeking radioisotope may also have usefulness or synergy with $^{153}$Sm-EDTMP against osteosarcoma.

Our patient population consisted of relapsed, resistant, and/or refractory patients with osteosarcoma bone lesions in palliative situations. Nevertheless, 8 of 14 had objective responses. To have more durable clinical responses, it probably will be necessary to follow similar principles as primary therapy of osteosarcoma whenever possible. These principles include (a) use of physical means for additional local control and (b) systemic control with chemotherapy. Principles learned from our study of $^{153}$Sm-EDTMP and gemcitabine for treatment of osteosarcoma may provide a useful new paradigm for treatment of other cancers with osteoblastic bone metastases.

## Acknowledgments

We thank Nancy Tuinistra; Denise Ganz; the nursing staff on station 72; the Pediatric transplant unit; the Pediatric Infusion Center; Dr. Brian Mullan and Bill Dunn in Nuclear Medicine and Mayo Clinic Orthopedic Oncology; consultants Drs. Frank Sim, Tom Shives, Mike Rock, and David Jacofsky; and Drs. Norm Jaffe, Val Lewis, Eugenie Kleinerman, and Robert Benjamin at the M.D. Anderson Cancer Center for their encouragement to continue osteosarcoma work at the M.D. Anderson.

## References

1. Goorin AM, Harris MB, Bernstein M, et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. J Clin Oncol 2002;20:426–33.
2. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol 2002;20:776–90.
3. Machak GN, Tkachev SI, Solovyev YN, et al. Neoadjuvant chemotherapy and local radiotherapy for high-grade osteosarcoma of the extremities. Mayo Clin Proc 2003;78:147–55.
4. DeLaney TF, Park L, Goldberg SI, et al. Radiotherapy for local control of osteosarcoma. Int J Radiat Oncol Biol Phys 2005;61:492–8.
5. Bacci G, Ferrari S, Bertoni F, et al. Campanacci M, Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the Istituto Ortopedico Rizzoli according to the Istituto Ortopedico Rizzoli/Osteosarcoma-2 protocol: an updated report. J Clin Oncol 2000;18:4016–27.
6. Ferguson WS, Goorin AM. Current treatment of osteosarcoma. Cancer Invest 2001;19:292–315.
7. Provisor AJ, Ettinger LJ, Nachman JB, et al. Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group. J Clin Oncol 1997;15:76–84.
8. Ozaki T, Flege S, Kevric M, et al. Osteosarcoma of the pelvis: experience of the Cooperative Osteosarcoma Study Group. J Clin Oncol 2003;21:334–41.
9. Bielack SS, Wulff B, Delling G, et al. Osteosarcoma of the trunk treated by multimodal therapy: experience of the Cooperative Osteosarcoma study group (COSS). Med Pediatr Oncol 1995;24:6–12.
10. Kawai A, Huvos AG, Meyers PA, Healey JH. Osteosarcoma of the pelvis. Oncologic results of 40 patients. Clin Orthop 1998;348:196–207.
11. Fagioli F, Aglietta M, Tienghi A, et al. High-dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian sarcoma group study. J Clin Oncol 2002;20:2150–6.
12. Chi SN, Conklin LS, Qin J, et al. Patterns of relapse in osteosarcoma: the Memorial Sloan-Kettering experience. Pediatr Blood Cancer 2004;42:46–51.

**13.** Goeckeler WF, Troutner DE, Volkert WA, Edwards B, Simon J, Wilson D. $^{153}$Sm radiotherapeutic bone agents. Int J Radiat Appl Inst B 1986;13:479–82.

**14.** Turner JH, Martindale AA, Sorby P, et al. Samarium-153 EDTMP therapy of disseminated skeletal metastasis. Eur J Nucl Med 1989;15:784–95.

**15.** Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. J Nucl Med 1993;34:1031–6.

**16.** Bayouth JE, Macey DJ, Kasi LP, Fossella FV. Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. J Nucl Med 1994;35:63–9.

**17.** Serafini AN. Samarium Sm-153 lexidronam for the palliation of bone pain associated with metastases. Cancer 2000;88:2934–9.

**18.** Brenner W, Kampen WU, Kampen AM, Henze E. Skeletal uptake and soft-tissue retention of $^{186}$Re-HEDP and $^{153}$Sm-EDTMP in patients with metastatic bone disease. J Nucl Med 2001;42:230–6.

**19.** Lattimer JC, Corwin LA Jr, Stapleton J, et al. Clinical and clinicopathologic response of canine bone tumor patients to treatment with samarium-153-EDTMP. J Nucl Med 1990;31:1316–25.

**20.** Aas M, Moe L, Gamlem H, Skretting A, Ottesen N, Bruland OS. Internal radionuclide therapy of primary osteosarcoma in dogs, using $^{153}$Sm-ethylene-diamino-tetramethylene-phosphonate (EDTMP). Clin Cancer Res 1999;5:3148–52s.

**21.** Franzius C, Bielack S, Sciuk J, Vollet B, Jurgens H, Schober O. High-activity samarium-153-EDTMP therapy in unresectable osteosarcoma. Nuklearmedizin 1999;38:337–40.

**22.** Franzius C, Bielack S, Flege S, et al. High-activity samarium-153-EDTMP therapy followed by autologous peripheral blood stem cell support in unresectable osteosarcoma. Nuklearmedizin 2001;40:215–20.

**23.** Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 2002;20:189–96.

**24.** Franzius C, Schuck A, Bielack SS. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 2002;20:1953–4.

**25.** Kinsella TJ, Glatstein E. Clinical experience with intravenous radiosensitizers in unresectable sarcomas. Cancer 1987;59:908–15.

**26.** Grunewald R, Kantarjian H, Keating MJ, Abbruzzese J, Tarassoff P, Plunkett W. Pharmacologically directed design of the dose rate and schedule of 2′,2′-difluorodeoxycytidine (gemcitabine) administration in leukemia. Cancer Res 1990;50:6823–6.

**27.** Abbruzzese JL, Grunewald R, Weeks EA, et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 1991;9:491–8.

**28.** Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 2003;21:3402–8.

**29.** McGinn CJ, Shewach DS, Lawrence TS. Radiosensitizing nucleosides. J Natl Cancer Inst 1996;88:1193–203.

**30.** Mason KA, Milas L, Hunter NR, et al. Maximizing therapeutic gain with gemcitabine and fractionated radiation. Int J Radiat Oncol Biol Phys 1999;44:1125–35.

**31.** Crane CH, Janjan NA, Evans DB, et al. Toxicity and efficacy of concurrent gemcitabine and radiotherapy for locally advanced pancreatic cancer. Int J Pancreatol 2001;29:9–18.

**32.** Eisbruch A, Shewach DS, Bradford CR, et al. Radiation concurrent with gemcitabine for locally advanced head and neck cancer: a phase I trial and intracellular drug incorporation study. J Clin Oncol 2001;19:792–9.

**33.** Wolff RA, Evans DB, Gravel DM, et al. Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. Clin Cancer Res 2001;7:2246–53.

**34.** Abbruzzese JL. New applications of gemcitabine and future directions in the management of pancreatic cancer. Cancer 2002;95:941–5.

**35.** Singh A, Holmes RA, Farhangi M, et al. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. J Nucl Med 1989;30:1814–8.

**36.** Goeckeler WF, Stoneburner LK, Kasi LP, Fossella FV, Price DR, Fordyce WA. Analysis of urine samples from metastatic bone cancer patients administered $^{153}$Sm-EDTMP. Nucl Med Biol 1993;20:657–61.

**37.** Bruland OS, Pihl A. On the current management of osteosarcoma. A critical evaluation and a proposal for a modified treatment strategy. Eur J Cancer 1997;33:1725–31.

**38.** Berrak SG, Pearson M, Berberoglu S, Ilhan IE, Jaffe N. High-dose ifosfamide in relapsed pediatric osteosarcoma: therapeutic effects and renal toxicity. Pediatr Blood Cancer 2005;44:215–9.

**39.** Bacci G, Forni C, Ferrari S, et al. Neoadjuvant chemotherapy for osteosarcoma. Intensification of preoperative treatment does not increase the rate of good histologic response to the primary tumor or improve the final outcome. J Pediatr Hematol Oncol 2003;25:845–53.

**40.** Smeland S, Muller C, Alvegard TA, et al. Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders. Eur J Cancer 2003;39:488–94.

**41.** Gorlick R, Meyers P. Osteosarcoma necrosis following chemotherapy: innate biology versus treatment-specific. J Pediatr Hematol Oncol 2003;25:840–1.

**42.** Koshkina NV, Kleinerman ES. Aerosol gemcitabine inhibits the growth of primary osteosarcoma and osteosarcoma lung metastases. Int J Cancer 2005;116:458–63.

**43.** Bruland O, Fodstad O, Funderud S, Pihl A. New monoclonal antibodies specific for human sarcomas. Int J Cancer 1986;38:27–31.

**44.** Anderson PM, Meyers DE, Hasz DE, et al. *In vitro* and *in vivo* cytotoxicity of an anti-osteosarcoma immunotoxin containing pokeweed antiviral protein. Cancer Res 1995;55:1321–7.

**45.** Larsen RH, Bruland OS. Intratumour injection of immunoglobulins labelled with the $\alpha$-particle emitter 211At: analyses of tumour retention, microdistribution and growth delay. Br J Cancer 1998;77:1115–22.

**46.** Gorlick R, Anderson P, Andrulis I, et al. Biology of childhood osteogenic sarcoma and potential targets for therapeutic development: meeting summary. Clin Cancer Res 2003;9:5442–53.

**47.** Cividalli A, Lividi E, Cecirelli F, et al. Combined use of gemcitabine and radiation in mice. Anticancer Res 2001;21:307–12.

**48.** McGinn CJ, Lawrence TS. Recent advances in the use of radiosensitizing nucleosides. Semin Radiat Oncol 2001;11:270–80.

**49.** O'Rourke TJ, Brown TD, Havlin K, et al. Phase I clinical trial of gemcitabine given as an intravenous bolus on 5 consecutive days. Eur J Cancer 1994;30:417–8.

**50.** Henriksen G, Breistol K, Bruland OS, Fodstad O, Larsen RH. Significant antitumor effect from bone-seeking, $\alpha$-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. Cancer Res 2002;62:3120–5.

Clinical Cancer Research

# Gemcitabine Radiosensitization after High-Dose Samarium for Osteoblastic Osteosarcoma

Peter M. Anderson, Gregory A. Wiseman, Linda Erlandson, et al.

*Clin Cancer Res* 2005;11:6895-6900.