Gemcitabine Radiosensitization after High-Dose Samarium for Osteoblastic Osteosarcoma

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Abstract

Osteoblastic metastases and osteosarcoma can avidly concentrate bone-seeking radiopharmaceuticals. We sought to increase effectiveness of high-dose $^{153}$Sm ethylenediaminetetramethylene phosphonate ($^{153}$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 ± 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 cell infusion 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$^2$/C2-4-5 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.

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)
syringe.153Sm-EDTMP (30 mCi/kg; 1,110 MBq/kg) was infused
EDTMP was thawed and placed into a 60-mL lead-shielded plastic
transfusions.

Before the153Sm-EDTMP infusion. Calcium gluconate (10%; 7.5 mg/kg
1,000-mg calcium carbonate was given orally every hour for 3 hours
highest specific activity. To decrease risk of symptomatic hypocalcemia,
scheduled on Wednesdays; thus, the high-dose infusion would have the
patient at the end of the infusion using 10 mL of 0.9% NaCl.
i.v. via a central line using small bore pediatric tubing to minimize
stimulating factor. All patients had central lines for153Sm-EDTMP
variety of chemotherapy regimens followed by granulocyte colony-
and indicator lesion(s) are in Table 2. Stem cells were harvested using a
consent was obtained in all patients after consultation including

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 153Sm-EDTMP
infusion, hydration, stem cell infusion, blood count monitoring, and
transfusions.

153Sm-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 153Sm-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/m²/h for 3 hours. 153Sm-
EDTMP was thawed and placed into a 60-mL lead-shielded plastic syringe.
153Sm-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 x 6 hours) were given and
i.v. hydration was continued for about 20 hours after the samarium infusion.

Gemcitabine administration. Antimetabolic therapy consisted of
granisetron (1 mg orally) and dexamethasone (8 mg orally). Gemcitabine (Gemzar; Lilly, Indianapolis, IN; 250 mg/m²/dose in the
first two patients using daily × 2, rest day, then daily × 2 patient 1; daily × 5 patient 2 and 1,500 mg/m² 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
153Sm-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 153Sm-EDTMP according to standard
clinical guidelines. Patients received routine supportive care including
red cell and platelet transfusions. Levofloxacin (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 computed 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 153Sm-EDTMP and gemcitabine as
described in Tables 2 and 3. Using 30 mCi/kg actual weight
calculation, an average of 1,640 mCi 153Sm-EDTMP was administered. The residual radioactivity before stem cell infusion (i.e., 14 days after high-dose 153Sm-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 perfor-
mance 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 cyto-
penias. 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 1. Properties and characteristics of 153Sm-EDTMP (Quadramet) |
|-----------------------------|---------------------|
| **Characteristic**          | **Property**        |
| Skeletal targeting          | Metabolized into bone and osteoblastic bone metastases |
| Bone seeking                | Bone/liver ratio = 700 |
| Radioactivity               |                      |
| \( \gamma \) (103 keV)      | 0.29 (suitable for imaging) |
| \( \beta \) (640 keV)       | 0.3 emissions/disintegration |
| \( \beta \) (710 keV)       | 0.5 emissions/disintegration |
| \( \beta \) (810 keV)       | 0.2 emissions/disintegration |
| Average \( \beta \) particle | 223 keV |
| Penetration                 | −1 mm |
| Half-life                   | 47 h |
| Source and synthesis        | Neutron irradiation of 162Sm, 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; 222,100 MBq/kg |
| Specific activity           | 20-46 mcg/mL |
| Organ distribution          | Bone >> marrow > bladder wall > kidney > liver = spleen = lung |
| Time of radioactive decay   | 9-13 d after high-dose 153Sm-EDTMP |
| decay to level, safe for    | (6-30 mCi/kg) Total body |
| hematopoietic stem cell     | radioactivity is <3.6 mCi |
| infusio |
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/C25. 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>
<thead>
<tr>
<th>Age/PS</th>
<th>Chemotherapy regimens</th>
<th>Number of prior indicator lesion(s)-type/location</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/1</td>
<td>2 (std*, I/E)</td>
<td>Metastatic pleural metastases (4)</td>
</tr>
<tr>
<td>16/1</td>
<td>3 (std, I/E, gem1)</td>
<td>Metastatic Frontal, left femur, lung</td>
</tr>
<tr>
<td>20/0</td>
<td>3 (std, I/E, T/C)b</td>
<td>Metastatic Spine (3)</td>
</tr>
<tr>
<td>17/2</td>
<td>3 (std, I/E, gem)</td>
<td>Metastatic R hilar (lung)</td>
</tr>
<tr>
<td>18/0</td>
<td>2 (std, I/E)</td>
<td>Metastatic R pelvis, lungs</td>
</tr>
<tr>
<td>24/1</td>
<td>4 (std, ifos/dox, HDMTX, gem)</td>
<td>Metastatic R tibia, lungs</td>
</tr>
<tr>
<td>14/1</td>
<td>3 (std, I/E, other)</td>
<td>Secondary R zygoma</td>
</tr>
<tr>
<td>17/0</td>
<td>2 (std, I/E)</td>
<td>Metastatic R tibia, lung</td>
</tr>
<tr>
<td>16/1</td>
<td>4 (std, I/E, aGM-CSF, gem)</td>
<td>Metastatic Spine</td>
</tr>
<tr>
<td>20/0</td>
<td>2 (std, I/E)</td>
<td>Unresectable R pelvis</td>
</tr>
<tr>
<td>12/1</td>
<td>2 (std, I/E)</td>
<td>Secondary L palate/maxilla</td>
</tr>
<tr>
<td>20/1</td>
<td>2 (std, ICE)</td>
<td>Recurrent Spine</td>
</tr>
<tr>
<td>14/0</td>
<td>2 (std, I/E)</td>
<td>Secondary Clivus</td>
</tr>
<tr>
<td>13/1</td>
<td>3 (std, I/E, cyclophosphamide/E)</td>
<td>Metastatic L pericardial/lingula</td>
</tr>
</tbody>
</table>

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.

Table 3. Samarium + gemcitabine + stem cell doses

<table>
<thead>
<tr>
<th>Patient</th>
<th>153Sm-EDTMP (total mCi)</th>
<th>Gemcitabine, dose (mg/m²)</th>
<th>Stem cell (PBPC), CD34+ × 10⁶/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,500</td>
<td>250 × 4 of 5 d</td>
<td>5.3</td>
</tr>
<tr>
<td>2</td>
<td>1,500</td>
<td>250 daily × 5</td>
<td>6.5</td>
</tr>
<tr>
<td>3</td>
<td>1,780</td>
<td>1,500 × 1</td>
<td>7.0</td>
</tr>
<tr>
<td>4</td>
<td>2,400</td>
<td>1,500 × 1</td>
<td>5.7</td>
</tr>
<tr>
<td>5</td>
<td>1,500</td>
<td>1,500 × 1</td>
<td>5.3</td>
</tr>
<tr>
<td>6</td>
<td>1,980</td>
<td>1,500 × 1</td>
<td>2.8</td>
</tr>
<tr>
<td>7</td>
<td>1,260</td>
<td>1,500 × 1</td>
<td>Marrow 1 × 10⁹ nuc/kg</td>
</tr>
<tr>
<td>8</td>
<td>1,900</td>
<td>1,500 × 1</td>
<td>Marrow 4.1 × 10⁹ nuc/kg</td>
</tr>
<tr>
<td>9</td>
<td>1,960</td>
<td>1,500 × 1</td>
<td>Marrow 5.6 × 10⁹ nuc/kg</td>
</tr>
<tr>
<td>10</td>
<td>1,200</td>
<td>1,500 × 1</td>
<td>6.0</td>
</tr>
<tr>
<td>11</td>
<td>1,080</td>
<td>1,500 × 1</td>
<td>1.8</td>
</tr>
<tr>
<td>12</td>
<td>1,880</td>
<td>1,500 × 1</td>
<td>5.4</td>
</tr>
<tr>
<td>13</td>
<td>1,275</td>
<td>1,500 × 1</td>
<td>3.0</td>
</tr>
<tr>
<td>14</td>
<td>1,840</td>
<td>1,500 × 1</td>
<td>2.0</td>
</tr>
<tr>
<td>Median</td>
<td>1,640</td>
<td></td>
<td>5.3</td>
</tr>
<tr>
<td>Mean</td>
<td>1,647</td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>SD</td>
<td>376</td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>SE</td>
<td>100</td>
<td></td>
<td>0.6</td>
</tr>
</tbody>
</table>

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 × 10⁶/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 ⁱ⁵³Sm-EDTMP + gemcitabine. Early and rapid improvement in bone scan uptake were seen in some patients.

**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 ⁱ⁵³Sm-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 ⁱ⁵³Sm has a half-life of 47 hours, our initial attempt was to use a low daily dose (250 mg/m²) 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/m² gemcitabine dose after samarium had no immediate significant side effects.5

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### Table 4. Residual radioactivity on d +14 s/p high-dose ⁱ⁵³Sm-EDTMP (30 mCi/kg)

<table>
<thead>
<tr>
<th>Patient</th>
<th>mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.76</td>
</tr>
<tr>
<td>2</td>
<td>1.10</td>
</tr>
<tr>
<td>3</td>
<td>1.01</td>
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<td>1.34</td>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>1.48</td>
</tr>
<tr>
<td>8</td>
<td>1.80</td>
</tr>
<tr>
<td>9</td>
<td>1.02</td>
</tr>
<tr>
<td>10</td>
<td>0.67</td>
</tr>
<tr>
<td>11</td>
<td>1.18</td>
</tr>
<tr>
<td>12</td>
<td>1.77</td>
</tr>
<tr>
<td>13</td>
<td>0.71</td>
</tr>
<tr>
<td>14</td>
<td>0.71</td>
</tr>
<tr>
<td>Median</td>
<td>1.03</td>
</tr>
<tr>
<td>Mean</td>
<td>1.08</td>
</tr>
<tr>
<td>SD</td>
<td>0.40</td>
</tr>
<tr>
<td>SE</td>
<td>0.11</td>
</tr>
</tbody>
</table>

5 Personal observations.
153Sm-EDTMP has very little washout after binding bone (35). Previous dosimetry measurements have shown organ/bone ratios with ~700-fold more 153Sm 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, 153Sm-EDTMP is the most specific agent commercially available for targeting osteoblastic metastases of osteosarcoma. 223Ra is a newer bone-seeking radioisotope that has α emission and is being developed in Norway (50). Because 223Ra is relatively marrow sparing compared with 153Sm-EDTMP, this bone-seeking radioisotope may also have usefulness or synergy with 153Sm-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 chemotheraphy. Principles learned from our study of 153Sm-EDTMP and gemcitabine for treatment of osteosarcoma may provide a useful new paradigm for treatment of other cancers with osteoblastic bone metastases.

Acknowledgments

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References

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