Myelotoxicity of samarium Sm 153 lexidronam in patients receiving prior treatment with chemotherapy or radiotherapy

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Background: The effect of prior treatment with radiotherapy and/or chemotherapy on the myelotoxicity of samarium lexidronam (Sm 153) in patients with metastatic bone lesions and bone pain was described.

Methods: Single-institution retrospective chart review of patients receiving Sm 153. The effect of Sm 153 on peripheral white blood cell (WBC), platelet counts, and change from baseline was calculated.

Results: The available hematologic data from records of 58 patients receiving 100 treatments with Sm 153 were reviewed. Prior treatment with radiotherapy or chemotherapy had no effect on changes from baseline or median nadir counts for either WBC or platelets when compared with patients not having such prior treatments. Multiple treatments with Sm 153 had no effect on change from baseline in WBC or platelet counts as compared with the initial administration. Median survival following the first dose of Sm 153 was 15 months.

Conclusions: Prior treatment with radiotherapy or chemotherapy did not affect the rates of myelotoxicity. Multiple treatments with samarium Sm 153 lexidronam also had no effect on severity of myelotoxicity with successive courses. Patients with bone predominant metastatic disease may survive for extended periods of time and may safely be treated with multiple modalities of therapy.

Key words: bone pain, metastasis, quadramet, radiopharmaceutical

Introduction

Bone metastases from solid tumors remain a significant source of morbidity in patients with cancer and represent a common manifestation of the disease. Bone metastases will develop in 65%–75% of patients with cancers of the breast and prostate, in 30%–40% of patients with lung cancer, and in significant proportions of patients with cancers of the thyroid, bladder, and kidney [1]. In patients with non-small-cell lung cancer, 70% of patients with bone metastases have bone pain [2] and 50% of all cancer pain is believed to be secondary bone metastases [3]. Moreover, this pain often requires treatment with progressively increasing doses of opioid analgesics often accompanied by side-effects including drowsiness, nausea and vomiting, and constipation. Radiotherapy is often highly effective for individual bony metastatic lesions, but its use may be limited in patients with widely metastatic bone disease and disparate areas of pain [4]. Although bisphosphonates have demonstrated their ability to reduce the incidence of skeletal-related events, their effect on bone pain is not as clearly defined.

In a randomized placebo-controlled study, although pain scores increased at a slower rate in patients receiving bisphosphonate treatment, both groups reported increasing pain scores over time [5]. Samarium Sm 153 lexidronam (QUADRAMET®, Cytogen Corporation, Princeton, NJ) is indicated for the relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan. When administered in combination with bisphosphonates, it has also demonstrated reductions in bone pain in patients with multiple myeloma, where bone disease is predominantly osteolytic in nature [6]. In two placebo-controlled clinical trials of patients with osteoblastic metastases [7, 8], treatment with samarium Sm 153 lexidronam significantly reduced pain scores and reduced analgesic use in patients with bone pain. In these studies, Samarium Sm 153 lexidronam demonstrated a low incidence of grade 3 or 4 bone marrow toxicity based on the National Cancer Institute’s Common Toxicity Criteria, with only 8% of patients experiencing grade 3 leukopenia and only 6% experiencing grade 3 thrombocytopenia. There were no instances of grade 4 leukopenia or thrombocytopenia among the 140 patients randomized to receive 1.0 mCi/kg of samarium Sm 153 lexidronam in these two placebo-controlled studies. Safety was further evidenced by small degrees of change from

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baseline in overall blood counts. In the first placebo-controlled study of samarium Sm 153 lexidronam which enrolled patients with a variety of primary malignancies metastatic to bone, the mean white blood cell (WBC) and platelet nadir counts were $3.1 \times 10^3/\mu l$ and $118 \times 10^3/\mu l$, respectively [7]. In a second placebo-controlled trial, in patients with bone metastases secondary to hormone-refractory prostate cancer, the mean WBC and platelet nadir counts were $3.8 \times 10^3/\mu l$ and $127 \times 10^3/\mu l$, respectively [8].

However, patients with multiple bone metastases are also candidates for treatment with radiotherapy and chemotherapy and there is little published data on the toxicity of samarium Sm 153 lexidronam in patients receiving these other treatment modalities. This study was therefore undertaken to examine the rates and severity myelotoxicity of samarium Sm 153 lexidronam in patients who had previously undergone treatment with radiotherapy and/or chemotherapy. In addition, the myelotoxicity of multiple treatments with samarium Sm 153 lexidronam was examined.

**Methods**

The records of all patients seen in the Department of Radiation Oncology at Magee-Womens Hospital who were treated with samarium Sm 153 lexidronam were reviewed. Age at the time of samarium Sm 153 lexidronam administration, dose of samarium Sm 153 lexidronam, pain response (where available), pretreatment samarium Sm 153 lexidronam and nadir WBC and platelet counts, date of death (if known), and prior treatment with chemotherapy and radiotherapy were recorded. Because many of the patients were referred from other hospitals and physicians, the dates of prior chemotherapy and their dose intensity were often not known, only the regimens. Patients had first, second, third or fourth-line chemotherapy for metastatic disease. Prior chemotherapy regimens included the combination of adriamycin, paclitaxel (Taxol, Bristol-Myer Squibb), fluorouracil, docetaxel (Taxotere, sanofi-aventis), navelbine, capetitabine, and a variety of hormonal agents such as tamoxifen, aromide, and bisphosphonates. The data were entered onto a spreadsheet (Excel, Microsoft Corp, Redmond, WA) and summarized using descriptive statistics (means and standard errors for proportions and medians and ranges for continuous variables). Differences in means were determined with the Student’s t-test and survival was estimated using the method of Kaplan and Meier [9].

**Results**

From January 2000 to September 2004, 58 patients received 100 treatments (range 1–8) with samarium Sm 153 lexidronam for which hematologic data were available. Patient characteristics are shown in Table 1. The majority of patients had metastatic breast cancer and received a dose of 1.0 mCi/kg of samarium Sm 153. Information on palliation was available for 69 courses of treatment. In 51 courses (74%), pain relief was scored as excellent or good.

**Effect of treatment with samarium Sm 153 on WBC and platelet counts**

Following treatment with samarium Sm 153 lexidronam, platelet counts decreased by 40% from a mean (± SE of the mean) of $259 \pm 9 \times 10^3/\mu l$ to $157 \pm 8 \times 10^3/\mu l$. However, of 99 treatments, only six treatments (6%) resulted in platelet counts that qualified as grade 3 toxicity, and only one treatment (1%) resulted in a platelet count that qualified as grade 4 toxicity, on the Common Terminology Criteria for Adverse Events (CTCAE).

Following treatment with samarium Sm 153 lexidronam, the WBC decreased by 30% from a mean (± SE of the mean) of $5.6 \pm 0.2 \times 10^3/\mu l$ to $3.7 \pm 0.2 \times 10^3/\mu l$. Of 100 treatments, no treatment resulted in a WBC that qualified as grade 4 toxicity, and only 11 treatments (11%) resulted in WBC counts that qualified as grade 3 toxicity on the CTCAE. These results are presented in Table 2.

**Effect of prior treatment with radiotherapy or cytotoxic chemotherapy on the WBC and platelet counts following treatment with samarium Sm 153 lexidronam**

The effect of prior treatment with radiotherapy or cytotoxic chemotherapy on changes in WBC and platelet counts is presented in Figure 1. Neither prior radiotherapy nor prior chemotherapy had a significant effect on platelet or WBC counts following treatment with samarium Sm 153 lexidronam. In fact, in these patients, the reduction in mean WBC and platelet counts were actually slightly less than those observed in patients who did not receive prior radiotherapy or cytotoxic chemotherapy. These data are presented in Table 3. Median

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Diagnosis (n)</th>
<th>Median age (range)</th>
<th>54.5 (36–86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Dose distribution of samarium Sm 153 (n)</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>1.0 mCi/kg</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Median total dose of samarium Sm-153 (mCi)</td>
<td>79.1</td>
<td></td>
</tr>
<tr>
<td>(± SE mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

SE, standard error.

### Table 2. The effect of treatment with samarium Sm 153 lexidronam on WBC and platelet counts

<table>
<thead>
<tr>
<th></th>
<th>Mean platelet counts (± SE) (×10^3/μl)</th>
<th>Mean WBC counts (± SE) (×10^3/μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>259 ± 9</td>
<td>5.6 ± 0.2</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>157 ± 8</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>Nadir as % of baseline</td>
<td>60%</td>
<td>66%</td>
</tr>
</tbody>
</table>

WBC, white blood cell; SE, standard error.
time to nadir for both the WBC and platelets is 28 days with recovery to baseline of 45 days.

effect of multiple treatments with samarium Sm 153 lexidronam on WBC and platelet counts
In the current study, 22 patients received more than one treatment with samarium Sm 153 lexidronam (range 2–8) for a total of 65 treatments. Once again, the change from baseline in WBC and platelet counts was less in patients who had received multiple doses of samarium Sm 153 lexidronam versus the change seen in patients receiving only a single dose. These data are presented in Table 4.

survival following treatment with samarium Sm 153 lexidronam
Although the prognosis is generally poor in patients with widely metastatic bone disease, survival in patients with bone-only disease may still be significant. The survival of 26 patients from first dose of samarium Sm 153 lexidronam for whom survival data were available is shown in Figure 2. The median survival of this group was 15 months, and some patients survived almost as long as 4 years. This prolonged survival also explains how a significant proportion of patients were able to receive multiple doses of samarium Sm 153 lexidronam.

discussion
It is not uncommon for patients with widely metastatic bone disease to require treatment with systemic chemotherapy or localized radiotherapy. In this study, of 100 total treatments with samarium Sm 153 lexidronam, 52 were preceded by localized radiation therapy and 61 by systemic chemotherapy. These prior therapies, however, appear to have had little or no effect on the WBC or platelet nadirs seen in these patients following their treatment with samarium Sm 153 lexidronam. Nadir levels and decreases from baseline were similar to or less than those previously reported. Multiple treatments with samarium Sm 153 lexidronam also had no significant effect on
its myelotoxicity. Consequently, samarium Sm 153 lexidronam can be administered in multiple courses provided that the platelet and WBC counts exceed $100 \times 10^3/\mu l$ and $2 \times 10^3/\mu l$, respectively.

There is very little literature on the use of bone-seeking radiopharmaceuticals administered in combination with chemotherapy. Samarium Sm 153 lexidronam has been administered with chemotherapy as part of a preparative regimen in patients receiving bone marrow transplants [10, 11] but in this setting, myelotoxicity is of little concern. Strontium-89 has been administered with chemotherapy in several studies in patients with metastatic prostate cancer. In one study, the combination of strontium-89, estramustine, and vinblastine resulted in grade 3/4 leukopenia and in grade 3/4 thrombocytopenia in 22% and 20%, respectively, of patients during the course of therapy. In only one patient, neutropenia associated with an infection [12]. In a second trial involving the use of strontium-89 and the combination of 5-fluorouracil, epirubicin, and mitomycin C (FEM) [13], the authors simply note that two of 18 patients receiving strontium-89 alone were hospitalized for ‘side effects’ whereas seven of 17 patients receiving the combination of strontium-89 and FEM were hospitalized. Unfortunately, the authors did not provide specifics of these toxic effects. In a third trial, strontium-89 was administered in combination with doxorubicin as consolidation therapy following an intensive chemotherapy induction regimen in 34 patients with hormone-refractory prostate cancer [14]. Five of these patients experienced bone marrow failure at a median of 23 months following treatment with strontium-89, although in two patients bone marrow biopsy revealed replacement of the marrow by tumor. An additional five patients developed bone marrow suppression with platelet counts <50 000/µl. This experience, following the intense chemotherapy regimen utilized, would have to be considered the exception, rather than the norm for the combination of radiopharmaceuticals and chemotherapy.

In summary, administration of samarium Sm 153 lexidronam following prior treatment with radiotherapy or chemotherapy was not associated with an increased risk of myelotoxicity. Similar results have been observed with the combination of chemotherapy and other radiopharmaceuticals used in the treatment of bone pain. Future studies should examine the effects of radiopharmaceuticals in combination with currently utilized chemotherapy regimens in patients with bone metastases, and such trials, examining the effects of samarium Sm 153 lexidronam in combination with a variety of chemotherapies, are currently underway.

**references**