Strontium-89 and Low-Dose Infusion Cisplatin for Patients with Hormone Refractory Prostate Carcinoma Metastatic to Bone: A Preliminary Report

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Strontium-89 has been used for the treatment of painful bony metastases in patients suffering from disseminated adenocarcinoma of the prostate, with a variable proportion of patients obtaining clinically significant reductions in analgesic requirements. Based on data revealing enhancement of continuous low-dose rate irradiation by low-dose cisplatin in murine models, a protocol using 148 MBq (4 mCi) of $^{89}$Sr and 35 mg/m$^2$ of cisplatin infused over 2 days, 1 and 4 wk after administration of the radioisotope was undertaken. Preliminary data suggest good pain relief with 55% of 18 patients entered thus far obtaining at least a 50% reduction in analgesic requirements. Improvements in total alkaline phosphatase and serum lactate dehydrogenase have consistently been seen, with some patients exhibiting improvements in hemoglobin, tumor markers and bone scans. Toxicity appears to be mild, with no life-threatening complications. In particular, myelosuppression after one course of treatment was modest, but retreatments in two patients has resulted in grade 3 hematologic toxicity. Two patients developed a "pain flare" after administration of cisplatin. Further accrual to this study will allow more accurate determination of pain response rate, and improved evaluation of parameters of objective response.


Prostate cancer is the second most common cancer among men in North America. Approximately 100,000 new cases are diagnosed, and about 28,000 patients will die of this cancer annually in the U.S. (1).

The natural history of metastatic (Stage D2) prostate cancer is well known. A median survival of patients after initial documentation of metastases has been reported to be 1.8 yr, depending on the characteristics of the patient population (2). Most patients relapse at some time after initial hormonal manipulation. Such patients usually develop painful bony metastases which require palliation, and have a median survival of between 4 and 8 mo (3). The management of patients with disseminated hormone-resistant prostate cancer is complicated by the lack of effective systemic agents. Further hormonal approaches are commonly attempted, but there is little evidence of benefit to patients from this form of treatment either in terms of survival or palliation (3). Although many trials using cytotoxic chemotherapy have been reported, there is no evidence of benefit to patients in terms of survival, and little evidence that this modality improves symptom control (3–5). Patients with hormone-resistant metastatic prostate cancer are currently treated with conventional analgesia, including narcotics, and external beam radiation therapy, both local and wide field (6).

Recently, intravenously administered radioisotopes have reemerged as a treatment modality for hormone-resistant prostate cancer (7). Strontium-89 ($^{89}$Sr), a beta-emitting radioisotope with a half-life of 50.6 days and a metabolism that is similar to that of calcium, has been shown in a number of studies to accumulate preferentially in areas of osteoblastic metastases. It has been shown to be effective in inducing pain relief, both subjectively and in reduction of analgesic requirements, with up to 57% of patients obtaining a 50% or greater reduction in analgesic dosages compared to pretreatment levels (7–9). Unfortunately many trials contain small numbers of patients and there is no consistent evidence that treatment with $^{89}$Sr results in objective evidence of tumor regression as measured by bone scan improvement, serum prostatic acid phosphatase (PAP) or prostate-specific antigen (PSA) levels, or other biochemical parameters. In addition, there is no convincing evidence that treatment with $^{89}$Sr results in improved survival in this patient population (7,8).
Blake et al. (10–12) have observed that absorbed radiation doses of 30–50 Gy to individual tumor deposits are achieved in patients with less than diffuse skeletal metastatic disease, with lower absorbed doses seen in patients with extensive skeletal metastases. Also, $^{90}$Sr may be retained longer at sites of metastases than in normal bone (11). This should result in an improved therapeutic ratio by delivering a substantial radiation dose to tumor while minimizing that delivered to normal tissue. Unfortunately, this positive gain may be undermined by the low dose rate (<4 eGy/hr) at which the radiation is delivered. Such low dose rates allow more time for repair of sublethal radiation injury and may be lower than the radiation doses required to counteract proliferation of tumor cells (13). The ultimate result could be less effective antitumor outcome.

Cisplatin, a chemotherapeutic agent used in a variety of tumors, increases the slope of radiation dose response curves in mammalian cells in vitro and enhances the radiation effect in tumor tissues and normal tissues in vivo (14). This seems to be the case for both hypoxic cells and oxygenated cells (15). In addition to modification of dose response curves, cisplatin also appears to inhibit the repair of sublethal radiation damage in split dose radiation experiments (14).

Studies by Fu and colleagues (16,17) examining the effects of continuous low-dose rate irradiation and concurrent infusion of chemotherapy drugs in murine models, have noted enhancement of radiation effect with cisplatin. The enhancement ratio after 10 Gy of continuous low-dose rate irradiation and concurrent cisplatin infusion was found to be in the range of 1.23 to 1.45. Based on the dose used in mice (16,18) in these studies (intraperitoneally implanted mini pumps infusing 11 mg/kg of cisplatin), the equivalent human dose would be approximately 32 mg/m² infused over 2 days. This dosage is well within the clinically tolerable dose range for this agent and with the exception of myelosuppression, cisplatin-associated toxicities do not overlap with those of $^{90}$Sr.

In view of the potential radio-enhancing effect of low-dose rate irradiation by cisplatin, it was felt that a trial combining $^{90}$Sr and cisplatin in the treatment of bony metastases resulting from hormone resistant prostate cancer would be of interest, both in terms of evaluating changes in pain symptomatology as well as other parameters, including objective tumor response. A Phase I/II trial was commenced, testing the combination of these two modalities, a preliminary report of which follows.

**MATERIALS AND METHODS**

**Patient Population**

Eligible patients must have histologically diagnosed adenocarcinoma of prostate metastatic to bone. At least one attempt at hormonal control of the tumor, either by orchietomy, or by medication (including stilbestrol, TACE, flutamide, cyproterone acetate, LHRH agonists, or any combination of the above) must have been made and have resulted in either progression of disease or failure to respond. The attempt at hormonal control of the tumor must have commenced at least 12 wk before consideration of entry onto this study. Patients must have multiple bone metastases documented by bone scanning or radiographs, of which at least two must be symptomatic. Patients must also be considered able to tolerate therapy with cisplatin and $^{90}$Sr and have a reasonable expectation of survival for at least 3 mo following therapy. An ECOG performance status of 3 (see Table 1) or better; WBC >3.5 × 10^9/liter, platelet count of >120 × 10^9/liter, serum creatinine <150 mmol/liter, creatinine clearance of ≥0.8 ml/sec, and bilirubin <20 mmol/liter were minimum requirements. Prior or concurrent malignancy of any other site or histology were ineligible unless the patient was disease-free for >5 yr, with the exception of nonmelanomatous skin cancer, which would be eligible at any time. Patients must not have received previous chemotherapy for wk prior to therapy. Patients with hemoglobin levels of <100 g/liter received, when possible, transfusion in order to attain a hemoglobin of approximately 100 g/liter, but anemia was not an ineligibility criteria per se. Patients must not have had extensive soft tissue involvement as a result of prostate cancer, although nonextensive, asymptomatic soft-tissue involvement such as lymphadenopathy, and uncontrolled disease in the prostate itself, were permitted. The patient must have given informed signed consent. This protocol was approved by the Review Board for Health Sciences Research involving Human Subjects, of the University of Western Ontario.

**Strontium-89 Administration**

Patients, once entered onto the trial, received $^{90}$Sr (Metastron, Amersham International) 148 MBq (4 mCi) on Day 1, by slow intravenous infusion over 5 min and were observed for 30 min following administration.

**Cisplatin Administration**

Patients were admitted to the general oncology ward on Day 8 and Day 29 to receive cisplatin. Intravenous hydration was given prior to receiving chemotherapy (0.9% sodium chloride with potassium chloride, 500 ml, over 2 hr), and patients were pretreated with dexamethasone, 10 mg, intravenously, metoclopramide, 0.5 mg/kg intravenously, and lorazepam 1 mg sublingually. Cisplatin, 5 mg/m², was given as a bolus at 1 mg/min, and immediately following this, an infusion of cisplatin 7.5 mg/m² in 500 ml of 0.9% sodium chloride over 12 hr was commenced and repeated three times for a total of 30 mg/m² infused over 48 hr. Concurrently, normal saline at 125 ml/hr and furosemide 20 mg orally twice daily were administered. Antinauseants were used as required, but no more than 1 dose of dexamethasone was permitted for each infusion of cisplatin. No dose modification for cisplatin were permitted for the Day 8 infusion, but for the

**TABLE 1**

<table>
<thead>
<tr>
<th>Eastern Cooperative Oncology Group (ECOG) Performance Status*</th>
</tr>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

Day 29 infusion, the dose of cisplatin was delayed one week for absolute granulocyte counts below $1.5 \times 10^9$/liter or platelet counts below $50 \times 10^9$/liter, with persistent myelosuppression resulting in omission of that dose.

**Patient Assessments**

Technetium-99m bone imaging was required at the time of injection of $^{89}$Sr, 1 mo after completing therapy (that is, after the final infusion of cisplatin) and monthly thereafter and computer stored for future analysis. Serum biochemistry, including lactate dehydrogenase (LD), total alkaline phosphatase (AP), prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA), were assayed before commencing treatment, before each course of cisplatin and monthly thereafter. Patients also underwent pain assessments and a review of their pain medication before starting treatment, and at each post-treatment assessment.

**Repeat Treatment**

Patients who, after completing therapy, obtained a good response in terms of pain control after their initial course of treatment with cisplatin and $^{89}$Sr, could, if they continued to meet the eligibility requirements, receive re-treatment using the same doses of $^{89}$Sr and cisplatin as described above if symptoms recurred. Re-treatments were delivered no less than 12 wk after initial $^{89}$Sr administration.

**Narcotic Score Assessment**

Patients on high potency narcotics (morphine, methadone, hydromorphone) as well as low to moderate potency narcotics (meperidine, codeine, and oxycodone) were assigned an equivalent parenteral morphine dosage based on narcotic conversion nomograms previously published (19). As well, nonnarcotic analgesic intake (such as acetaminophen and non-steroidal anti-inflammatory agents) was noted.

**Response Criteria**

Patients were noted to have complete disappearance of pain if subjectively the patient felt himself to be pain-free and had discontinued taking all analgesics. A partial pain response was said to have occurred if the patient had dramatic improvement in pain and had a decrease in dosage of at least 50% in both narcotic and nonnarcotic analgesics. Bone scans were initially graded using criteria described by Soloway et al. (20), and all lesions were reviewed for changes in size, distribution and intensity relative to normal bone. PSA and PAP were noted to be stable if a change of no more than 15% was noted.

**Toxicity**

Toxicity was graded according to the Cooperative Group Common Toxicity Criteria Scale (21).

**Statistical Analysis**

Differences between pre- and post-treatment tumor marker levels, as well as biochemical values were analyzed by the Wilcoxon signed rank test. Associations between post-treatment results and pain relief were analysed using Fisher's exact test. All p values are two-tailed.

**RESULTS**

**Patients**

Eighteen patients have been accrued to this study and all are considered evaluable for pain response. All patients had objective evidence of progression despite hormonal therapy (minimum duration: 6 mo) and most patients underwent more than one attempt at hormonal control. Seventeen patients completed all components of therapy: one patient did not receive a second infusion of cisplatin due to the development of obstructive uropathy secondary to retroperitoneal lymphadenopathy and declined all further treatment. An additional patient completed two courses of cisplatin but did not return for follow-up due to the rapid development of symptomatic pulmonary metastases. Post-treatment biochemical and bone scan data are therefore available on 17 and 16 patients, respectively. Pretreatment characteristics are summarized in Table 2. Thus far, four of these patients have undergone retreatment with $^{89}$Sr on this protocol.

**Pain Relief**

Four patients (22%) have been able to discontinue their pain medication completely and were pain-free after treatment on this protocol. Duration of analgesia and pain-free status ranged from 1 to 4 mo (median: 4 mo). Six patients (33%) obtained substantial pain relief associated with a $>50\%$ reduction in dosage of all pain medication, including non-narcotic analgesia. The duration of this benefit ranged from 1 to 3 mo (median: 2 mo). This results in a complete and partial pain relief rate of 55% for this trial thus far. Four patients had improved pain control with less than 50% analgesic reduction, three patients experienced no change in either pain or analgesic usage, and one patient experienced progressive pain requiring additional analgesia. Statistically significant decreases in narcotic intake were noted with most patients discontinuing narcotic

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**TABLE 2**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
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<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Median: 71</td>
</tr>
<tr>
<td>Range: 57–74</td>
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<tr>
<td>ECOG performance status</td>
</tr>
<tr>
<td>1:10</td>
</tr>
<tr>
<td>2:8</td>
</tr>
<tr>
<td>3:0</td>
</tr>
<tr>
<td>Time to entry post-initial diagnosis (yr)</td>
</tr>
<tr>
<td>Median: 2</td>
</tr>
<tr>
<td>Range: 0.5–5</td>
</tr>
<tr>
<td>Prior therapy</td>
</tr>
<tr>
<td>Surgery: 2</td>
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<tr>
<td>Radiotherapy: 12</td>
</tr>
<tr>
<td>Hormones: 18</td>
</tr>
<tr>
<td>$^{89}$Sr: 1</td>
</tr>
<tr>
<td>Time on hormone therapy (yr)</td>
</tr>
<tr>
<td>Median: 2</td>
</tr>
<tr>
<td>Range: 0.5–5</td>
</tr>
<tr>
<td>Number of hormone manipulations</td>
</tr>
<tr>
<td>Median: 2</td>
</tr>
<tr>
<td>Range: 1–4</td>
</tr>
<tr>
<td>Bone scan score (EOD) (20)</td>
</tr>
<tr>
<td>Median: III</td>
</tr>
<tr>
<td>Range: III–IV</td>
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<tr>
<td>Soft-tissue involvement: 6</td>
</tr>
</tbody>
</table>
therapy; however, many of these continued to take non-narcotic analgesia (see Table 3).

**Bone Scans**

Sixteen patients have had follow-up bone scans; two patients did not have repeat bone scanning due to early death. Two patients have had an improvement on bone scans with all lesions exhibiting a diminution of technetium uptake. This was maintained for 2+ and 4 months, respectively. Mixed responses were seen in three patients (one diminution of uptake in a number of metastases with others unchanged, one complete disappearance of previously documented metastases with the development of new lesions, and one a mixture of progression and regression of previously bony metastases). Three patients have had clear evidence of progression of known metastatic disease, and eight patients had stable bone scans after therapy.

**Serologic Parameters**

Table 3 describes changes in total AP, LD, PSA and PAP seen at first follow-up. All but one patient revealed a decrease in AP compared to pretreatment values, although two further patients exhibited a transient increase in the enzyme one week after $^{89}$Sr administration. LD similarly decreased in all but two patients compared to pretreatment values. The differences between pre- and post-treatment values were statistically significant for both enzymes. Table 3 also describes the changes in both PSA and PAP with treatment on this protocol. No statistically significant differences were found when examining pre- and post-treatment levels of either tumor marker. Eighteen percent of patients achieved a greater than 50% decrease in both PSA and PAP at first follow-up (2 mo after $^{89}$Sr administration). All three patients with decreases of greater than 50% in PAP or PSA obtained complete or partial pain relief, but the association was not significant (Fisher's exact test, $p > 0.2$).

**Hemoglobin**

Six patients achieved increases in hemoglobin ranging from 10 to 20 g/liter (median: 18.5 g/liter). One patient was transfused from a hemoglobin level of from 68 g/liter to 114 g/liter prior to commencing treatment. While receiving therapy, his hemoglobin dropped to 99 g/liter, but then increased to 134 g/liter without further transfusion and was maintained for 4 mo. Increased hemoglobin levels were maintained for 2–4 mo in those patients demonstrating increases. Five of the patients with increased hemoglobin levels obtained at least partial pain relief, and this association was significant (Fisher's exact test, $p < 0.05$).

**Toxicity**

Table 4 denotes toxicities identified for patients receiving their first course of treatment with $^{89}$Sr and cisplatin. Three patients developed grade 2, and one patient grade 3, granulocytopenia, with only one patient developing grade 3 thrombocytopenia. No platelet transfusions were required. One patient developed grade 2 vomiting during his first course of cisplatin infusion, but this resolved and did not recur with the subsequent cisplatin infusion. Two patients developed a "pain flare" 36–48 hr after administration of $^{89}$Sr. Interestingly, two other patients developed a similar "pain flare" 24 and 48 hr after completing their first course of cisplatin, with one patient requiring hospitalization for pain control. All four cases of "pain flare" resolved within 48 hr, and in each case, was associated with complete or partial pain relief, although this association did not reach statistical significance (0.05 < $p < 0.1$).

**Repeat Treatments**

Four patients have received re-treatment on this protocol. One patient required a 1-wk delay in the administration of the second cisplatin infusion due to grade 3 granulocytopenia, and one patient required omission of the second infusion of cisplatin altogether due to grade 3 thrombocytopenia (nadir 32 × 10$^3$/liter) which was persistent. A third patient developed grade 2 granulocytopenia but required no delays in treatment. No platelet transfusions were required. Each of the patients who were retreated had obtained a period of complete pain relief with their initial $^{89}$Sr and cisplatin therapy. Three patients who received retreatment again achieved complete pain relief.

### Table 3

<table>
<thead>
<tr>
<th>(A) Nonspecific Parameters</th>
<th>Pretreatment</th>
<th>Post-treatment</th>
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<tbody>
<tr>
<td></td>
<td>Mean/Median</td>
<td>Mean/Median</td>
</tr>
<tr>
<td>AP (u/liter)</td>
<td>796/286</td>
<td>402/206</td>
</tr>
<tr>
<td>LD (u/liter)</td>
<td>370/270</td>
<td>256/144</td>
</tr>
<tr>
<td>Narcotic score (mg/d)</td>
<td>22.6/12</td>
<td>14.9/0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B) Tumor Markers</th>
<th>Decrease</th>
<th>Stable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&gt;50%)</td>
<td>(15–50%)</td>
</tr>
<tr>
<td>PSA</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>PAP</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total WBC</th>
<th>Granulocytes</th>
<th>Platelets</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

(Grade 2: Total WBC 2.0–2.4 × 10$^9$/liter; granulocytes: 1.0–1.4 × 10$^9$/liter; platelets: 50–74.9 × 10$^9$/liter; nausea: intake significantly decreased but can eat; Grade 3: Total WBC 1.0–1.9 × 10$^9$/liter, granulocytes 0.5–0.9 × 10$^9$/liter, platelets 25.0–49.9 × 10$^9$/liter; nausea: no significant intake).
for 2 mo. One patient obtained excellent partial relief of pain, with improved pain control, and a 67% reduction in morphine intake lasting 2 mo.

**Survival**

Thus far, 3/18 patients entered into the study have died. Two developed uncontrolled pulmonary metastases, and one patient developed bilateral ureteric obstruction secondary to lymphadenopathy after the first cisplatin infusion; further therapy was declined. Survival on this trial ranges from 1 to 12+ mo (median 8+ mo) from initial \(^{89}\)Sr injection.

**DISCUSSION**

A number of studies, both single arm and randomized controlled trials, have been reported in the utilization of \(^{89}\)Sr in various doses in the treatment of painful bony metastases associated with adenocarcinoma of the prostate (12,22–34). The main outcome measured in these studies is the degree of pain relief afforded subjects with metastatic prostate carcinoma resistant to hormone therapy. Other studies determined rates for complete pain relief of 6%–50% for evaluable patients (0%–44% for all entered subjects). The degree to which less complete pain relief is obtained is less well characterized, due to the variable and often poorly defined response criteria used in these trials. When the partial response is defined as a marked reduction in pain, reducing analgesic requirements to at least 50% of pretreatment levels, the percentage of patients achieving either complete or partial pain relief varies between 6% and 60% for evaluable subjects (0%–57% for all entered patients) (8,35). Additional patients may have had lesser degrees of pain relief. The wide range of responses may partially be explained by the small numbers of patients accrued to some trials (25,27), and the large number of patients considered un evaluable in other studies (34). Also, most trials fail to adequately describe the extent of bony metastases in patients treated with radioisotopic therapy. This results in additional difficulty in making comparisons between trials, as well as within trials that are conducted at a number of centers which may treat patients with different extents of disease (24).

Objective measures of tumor response to \(^{89}\)Sr are only occasionally seen. Although some investigators have noted improved bone scans after treatment, most patients exhibit either stable bone scans (34) or overall progressive disease (27). Kloiber et al. (25) evaluated six patients with focal metastases and noted decreases in the relative intensity of focal lesions in 80% of lesions selected for measurements, employing digitalized images of abnormal as well as normal areas from bone scans. These changes did not correlate with pain relief, although three patients had some decrease in pretreatment acid phosphatase levels. This method is likely to be much more sensitive than visually grading improvement in lesions, although it may be more reproducible. Only occasional decreases in acid phosphatase levels have been noted in other studies (26). Aside from two small studies (28,30) the use of \(^{89}\)Sr has yet to yield a beneficial effect in this group of patients in terms of overall survival.

Although \(^{89}\)Sr appears to be an effective agent in inducing important degrees of pain relief as well as meaningful decreases in oral analgesic intake, it is clear that a relative minority of patients treated achieve substantial pain relief through the use of this agent, and objective evidence of tumor regression occurs only occasionally. These results are the stimulus for new investigative strategies designed to improve the efficacy of this agent.

This study was initiated based on laboratory data that suggest that cisplatin possesses radioenhancing effects with the use of low-dose rate irradiation. Since cisplatin and \(^{89}\)Sr share myelosuppression as a potential toxicity, the toxicity generated by the combination of these two agents could potentially limit the usefulness of this therapy. Thus far, toxicity has been mild and manageable. For patients receiving their first course of treatment with \(^{89}\)Sr and cisplatin, myelosuppression did not prevent completion of therapy, did not result in additional complications such as bleeding or neutropenic sepsis and appeared to be well tolerated. At the dosage used, no otoxicity, peripheral neuropathy or nephrotoxicity were found, and chemother-apy-associated nausea was modest. The occasional development of “pain flare” reactions after the administration of cisplatin rather than after \(^{89}\)Sr is interesting and is possibly related to the radioenhancement of \(^{89}\)Sr by cisplatin at bony metastatic sites.

Three patients (18%) have obtained decreases in PAP and PSA of greater than 50%. These results compare favorably with other systemic treatments, such as the investigational agent suramin (36), especially in view of the single month of therapy with \(^{89}\)Sr and cisplatin compared with prolonged treatment with other, more toxic systemic agents. As noted in other papers employing \(^{89}\)Sr as a single agent (26), declines in prostate cancer tumor markers are an unusual event in studies, partly as a result of continued tumor marker production by areas of soft-tissue disease. Nevertheless, the possibility that decreases in PAP might be associated with pain response is interesting. Other investigators have noted declines in total AP levels (25,34) in patients treated with \(^{89}\)Sr, but no numerical values were provided in these reports. One study noted increases in alkaline phosphatase levels in four of six patients treated with 0.8 MBq/kg of \(^{89}\)Sr, but it is unclear when the post-treatment samples were taken in relation to the administration of radioisotope (22). In the present study, all but one patient had decreases to some extent in total AP levels. These, however, could not be correlated with response.

A number of patients have demonstrated improvement in terms of tracer uptake on post-treatment bone scans. These results are promising, but patient numbers remain too low to draw firm conclusions.
Serum LD (particularly isoenzymes 4 and 5) are frequently elevated in advanced prostate cancer (37–39). When the disease is still hormone-responsive and effective hormonal therapy is instituted, these values often return to normal (37). Out of 17 patients in the present trial for whom data are available, 15 patients had declines in serum LD levels. Thus far, no other trials have commented in detail on changes in serum LD as a result of $^{89}$Sr therapy. We suggest that investigators utilizing radioisotopes in the treatment of metastatic prostate cancer carefully evaluate serologic markers including non-specific markers such as LD and AP.

Cisplatin has been associated with the development of anemia (40), and patients with progressive prostate carcinoma often develop normocytic normochromic anemia of significant degree. In this study, six patients developed increases in hemoglobin that were sustained for some months. This result may relate to reduced tumor burden with consequent relief of anemia of chronic disease, or possibly an improvement in the degree of marrow infiltration with tumor cells.

The patients entered into this trial are fairly representative of patients with advanced metastatic hormone-resistant prostate carcinoma. Three patients have died, and the survival thus far appears promising. However, a randomized, controlled clinical trial will be required to determine if this form of therapy has any survival benefit to patients over and above best supportive care or $^{89}$Sr alone. Retreatment of patients on this protocol with $^{89}$Sr and cisplatin has resulted in more myelosuppression than has been seen with the initial course of treatment. This may reflect progressive disease and marrow failure, as well as persistent $^{89}$Sr effects on bone marrow function. Repeat therapy with $^{89}$Sr has resulted in myelosuppression that is occasionally persistent (8,41), and investigators utilizing $^{89}$Sr in regimens in which repeat courses of the radioisotope are administered should proceed with caution.

Thus far, this regimen appears to be relatively safe and effective for the treatment of disseminated painful bony metastases resulting from adenocarcinoma of the prostate. The small sample size reported thus far makes correlations between objective tumor response and pain relief difficult and further accrual of data will help to determine the actual response rate in terms of pain control, bone scan improvement and serum marker reduction, as well as survival. However, single arm studies may be subject to important differences in terms of the pretreatment characteristics of entered patients, and only through well-designed randomized controlled trials will the benefits of radiosensitization of $^{89}$Sr therapy through the use of cisplatin, if any, be adequately demonstrated.

REFERENCES


**SELF-STUDY TEST**

Radiobiology and Radiation Protection

Questions are taken from the Nuclear Medicine Self-Study Program I, published by The Society of Nuclear Medicine

**DIRECTIONS**

The following items consist of a heading followed by lettered options related to that heading. Select the one lettered option that is best for each item. Answers may be found on page 1477.

For each source of radiation exposure to the U.S. population (items 1-5), select the most correct estimate of the magnitude of annual exposure dose by comparison with natural background radiation (answers A-E).

A. background exposure (BE)
B. 50% BE
C. 15% BE
D. 5% BE
E. 1% BE

1. diagnostic x-ray
2. nuclear medicine procedures
3. nuclear power
4. consumer products
5. fallout from weapons testing

For each type of acute effect caused by whole-body radiation exposure in humans (items 6-9), select the lowest radiation dose (A-E) that could be expected to elicit the effect.

A. 50 rads
B. 200 rads
C. 350 rads
D. 1250 rads
E. 5000 rads

6. the prodromal syndrome
7. lethality
8. the LD50
9. seizures and coma

For each of the radiation-related responsibilities listed (items 10-13), select the appropriate advisory group or federal agency (A-E).

A. Nuclear Regulatory Commission (NRC)
B. Food and Drug Administration (FDA)
C. Environmental Protection Agency (EPA)
D. National Council on Radiation Protection and Measurements (NCRP)
E. Center for Devices and Radiological Health (CDRH)

10. Responsible for deciding whether a new radiopharmaceutical should be approved for use in humans
11. Establishes radiation protection standards for use in clinical nuclear medicine
12. The lead agency for the U.S. government for the establishment of federal radiation protection policy
13. Regulates the use of radioactive materials for research in humans under the auspices of the Radioactive Drug Research Committee (RDRC)

ICRP Publication 26 recommends a number of significant changes in the radiation protection guidelines that concern nuclear medicine. These recommendations form the basis of proposed changes in Part 20 of Title 10 of the Code of Federal Regulations. Which of the following are recommendations of ICRP Publication 26?

14. Adoption of a de minimis dose level of 1 mrem for occupational exposure
15. Elimination of 5(N - 18) formula for calculating permissible lifetime doses
16. Abandonment of the critical organ concept in favor of a weighted total body dose equivalent that takes into account irradiation of all radiosensitive organs and tissues
17. Addition of doses received from internally deposited radionuclides to those from external irradiation in determining the total effective dose equivalent

The decision to administer potassium iodide (KI) to populations after a nuclear reactor accident is based on

18. the expectation that thyroid doses in the exposed population will exceed 500 mrem.

(continued on page 1477)