# Effects of Low-Dose Cisplatin on [89]Sr Therapy for Painful Bone Metastases from Prostate Cancer: A Randomized Clinical Trial

Rosa Sciuto, MD; Anna Festa, MD; Sandra Rea, MD; Rosella Pasqualoni, MD; Serenella Bergomi, MD; Germana Petrilli, MD; and Carlo L. Maini, MD

*Nuclear Medicine Department, Regina Elena Cancer Institute, Rome, Italy*

This study evaluated the effects of low-dose cisplatin plus ^{89}Sr versus ^{89}Sr alone in the treatment of painful bone metastases from prostate cancer, addressing both pain palliation and cytostatic effects. **Methods:** Seventy patients with metastatic hormone-refractory prostate cancer were randomized into 2 groups: One group (arm A) received 148 MBq ^{89}Sr plus 50 mg/m$^2$ cisplatin, and the other group (arm B) received 148 MBq ^{89}Sr plus placebo. After treatment, the patients were followed up until death to evaluate the outcome variables: grade and duration of pain palliation, onset of new painful sites, changes in bone disease, global survival, serum prostate-specific antigen and alkaline phosphatase changes, and hematologic toxicity. **Results:** Overall pain relief occurred in 91% of patients in arm A and 63% of patients in arm B ($P < 0.01$), with a median duration of 120 d in arm A and 60 d in arm B ($P = 0.002$). New painful sites on previously asymptomatic bone metastases appeared in 14% of patients in arm A and in 30% of patients in arm B ($P = 0.18$). The median survival without new painful sites was 4 mo in arm A and 2 mo in arm B ($P = 0.04$). Bone disease progression was observed in 27% of patients in arm A and in 64% of patients in arm B ($P = 0.01$). Median global survival after therapy was 9 mo in arm A and 6 mo in arm B ($P = 0.30$). Transient and moderate hematologic toxicity, as determined by World Health Organization criteria, was apparent in both arms without significant differences. **Conclusion:** The addition of a low dose of cisplatin enhances the effect of a standard dose of ^{89}Sr without significant side effects, producing a significant improvement in pain palliation and a cytostatic effect on bone disease.

**Key Words:** strontium; cisplatin; pain palliation; prostate cancer

**J Nucl Med 2002; 43:79–86**

**P**ainful bone metastases are a challenging problem in the management of patients with hormone-refractory prostate cancer because of its high prevalence and high morbidity (*1,2*). Effective palliative treatment of painful bone metastases is a key therapeutic goal in these patients, aiming at improving their quality of life. External-beam irradiation, although effective on localized lesions, cannot routinely be used in the treatment of diffuse or multifocal bone disease because hemibody irradiation is associated with significant marrow toxicity (*3*). Chemotherapy has not shown encouraging results in metastatic prostate cancer (*4*), and the efficacy of the pharmacologic approach with analgesics is limited by drug tolerance and adverse effects when drugs are used at high doses and for prolonged periods (*5*).

Radionuclide therapy with ^{89}Sr-chloride (^{89}Sr) is an effective alternative for bone pain in prostate cancer, producing a palliation rate of 51%–96% (*6–9*). Despite these encouraging results some problems remain to be clarified, such as the significant percentage of unresponsive patients (up to 30%), the low complete response rate (up to 20%), and the effect on bone disease progression (*6*). Although total target doses for ^{89}Sr are quite high, up to 5,000 cGy using a standard dose of 148 MBq (*10,11*), the dose rate at which the radiation is delivered is low, <4 cGy/h (*12*), and may limit ^{89}Sr efficacy by allowing repair of sublethal radiation injury and being insufficient to counteract proliferation of tumor cells (*13*).

Preliminary strategies for increasing the response rate to ^{89}Sr have been devised using platinum-mediated radiosensitization of cancer cells, but these preliminary encouraging results have not yet been validated in a randomized clinical trial (*12,14,15*). This article reports a randomized phase III clinical trial evaluating the effects of low-dose *cis*-diamminedichloroplatinum (II), or cisplatin, plus ^{89}Sr versus the effects of ^{89}Sr alone in the treatment of 70 prostate cancer patients with painful bone metastases.

## MATERIALS AND METHODS

### Study Design

The study was a phase III prospective clinical trial. It was controlled, randomized, and masked and was approved by the local Ethic Committee. Eligible patients were randomized into 2 groups receiving different treatment: One (arm A) received the treatment to be tested (^{89}Sr plus cisplatin); the other (arm B) received ^{89}Sr plus placebo and served as the control group. Each patient gave written informed consent.

A data manager randomly allocated patients to either arm by applying a previously established algorithm to a set of random numbers. Patients were also randomized separately into 2 strata to avoid confounding effects from different baseline clinical conditions. Subdivision of patients into the 2 strata was based on their general condition and their performance status score on the Karnofsky Scale. Stratum 1 included patients with a mildly impaired general condition and a Karnofsky score of 60–100. Stratum 2 included patients with a strongly impaired general condition and a Karnofsky score of 10–50. Neither patients nor clinicians knew the group to which patients had been assigned, ensuring a correct double blinding of the study and avoiding confounding factors during follow-up. Pain palliation, cytostatic effect, and marrow toxicity were the endpoints addressed.

## Patients

Seventy patients (age range, 51–89 y; mean age, 69 y) with bone metastases from histologically proven prostate cancer entered the study after a baseline clinical examination and were randomized into the 2 arms, each containing 35 patients. Eleven patients had been treated by chemotherapy, 20 by local external-beam radiotherapy, and 6 by both. A minimum of 6 mo had elapsed after the completion of previous chemotherapy or radiotherapy. Hormone therapy had not been altered in the previous 3 mo and was continued without change during the study. All patients had hormone-resistant disease that was progressing after being treated with at least 2 hormone schedules.

Patients were enrolled into the study according to the usual eligibility criteria, as previously defined (16). Patients were excluded if they had difficulty complying with the follow-up schedule or had suspected disseminated intravascular coagulation or evidence of spinal cord compression.

## Baseline Evaluation

Before randomization, all enrolled patients underwent a complete clinical evaluation to measure baseline pretherapy variables: age, hematologic and renal function, serum alkaline phosphatase (AP) level, prostate-specific antigen (PSA) level, and performance status score on the Karnofsky Scale. Pain was evaluated by a 5-point score assigned using a modified Wisconsin test (16) and by a pain map illustrating the number and topography of painful sites. Bone disease was assessed by $^{99m}$Tc-methylene diphosphonate bone scanning, with assignment of a 5-point scintigraphic score based on the number or extent of metastases according to the criteria of Soloway et al. (17). All bone scanning was performed, and the results classified, by well-trained nuclear physicians at our institute.

## Treatment Protocol

*Arm A.* Two short hospitalizations, at an interval of 10 d, were required for each patient. In the first hospitalization, a slow intravenous cisplatin infusion (Cisplatino Teva; Teva Pharma, Milan, Italy) of 18 mg/m$^2$ in 1,000 mL 0.9% sodium chloride solution plus 20 mg furosemide was administered over 3 h. At the end of the infusion, 148 MBq $^{89}$Sr (Metastron; Nycomed-Amersham International, Buckinghamshire, U.K.) were injected as a bolus (day 0). In the second hospitalization, an intravenous cisplatin infusion of 16 mg/m$^2$ in 1,000 mL 0.9% sodium chloride solution plus 20 mg furosemide was administered over 6 h (day 10) and repeated the day after (day 11), for a total cisplatin dose of 32 mg/m$^2$ infused over 48 h. Standard support consisting of intravenous hydration, steroids, and antiemetic drugs was used during both treatments.

*Arm B.* The protocol was the same as for arm A, except that a placebo infusion (1,000 mL 0.9% sodium chloride solution plus 20 mg furosemide) was administered in place of the cisplatin infusion.

## Patient Follow-Up

After treatment, follow-up continued until the patient's death, and the following variables were monitored at predetermined intervals: hematologic and renal function, AP and PSA serum levels, pain score, pain map, bone scan findings, and Karnofsky performance score.

## Data Analysis

*Pain Palliation.* This outcome was evaluated 2 mo after $^{89}$Sr administration and was defined as positive (responders) if the pain score improved or negative (nonresponders) if it did not (16). A positive outcome was characterized on the basis of grade and duration of pain palliation. Grade was classified as complete response, partial response, or minimal response (16). Duration (survival time free of pain relapse) was determined by considering a worsening of the pain score to be a marker of the end of the palliative effect. The onset of new painful sites on previously asymptomatic bone metastases was also considered a pain palliation variable. Accordingly, the following factors were evaluated: for both arms of the study, the prevalence of patients presenting with new painful sites; for each arm of the study and each patient, the number of observed sites; and the survival time without onset of new painful sites.

*Cytostatic Effect.* This outcome was evaluated by classifying changes in bone disease and global survival. Bone disease was classified as showing a partial response, stability, or progression according to the National Prostate Cancer Project criteria for stage D$_2$ prostate cancer (18). Global survival after therapy was evaluated as survival free of pain relapse plus survival after pain relapse and was illustrated by Kaplan–Meier curves. All deaths, both tumor related and tumor unrelated, were included in the analysis. In addition, changes in AP and PSA serum levels were evaluated as indirect measures of cytostatic effect.

*Marrow Toxicity.* This outcome was evaluated by measuring changes in platelets, leukocytes, and hemoglobin during the first 3 mo of follow-up and was classified by a 5-point toxicity score according to World Health Organization (WHO) criteria (19).

## Statistical Analysis

Outcome variables (responders and response grade, new painful sites, and bone disease progression) were compared by the $\chi^2$ test. Survival times (survival free of pain relapse, survival without new painful sites, survival after pain relapse, and global survival after therapy) were assessed by Kaplan–Meier curves and compared by the log-rank test. Differences in pretherapy variables between the 2 arms were assessed by the *t* test for paired data or by the $\chi^2$ test, as appropriate, whereas differences between pretherapy and posttherapy variables in each arm were evaluated by the *t* test with Bonferroni adjustment and by the Wilcoxon signed rank test, as appropriate.

For ease of analysis, exact *P* values are reported. The level of significance was set at the conventional value of $P < 0.05$, and probability values just slightly greater than the $\alpha$ value of 0.05 were considered marginally significant (20). Confidence intervals (CIs) were also evaluated.

## RESULTS

Patient baseline characteristics for each arm of the study are presented in Tables 1 and 2. No significant differences were observed in baseline variables between the 2 arms.

### Pain Palliation

Overall pain relief occurred in 32 patients of arm A and in 22 patients of arm B (91% and 63%, respectively; $P <$ 0.01). The grade of pain palliation in the 2 arms is reported in Table 3. Clinically evident pain relief occurred within 1 mo, with a median onset at 15 d in both arms. Survival free of pain relapse ranged from 1 mo to 1 y in arm A and from 1 to 7 mo in arm B (Fig. 1A). The mean duration of pain palliation was 134 d in arm A and 68 d in arm B, with a median of 120 and 60 d, respectively ($P = 0.002$).

The percentage of patients presenting with new painful sites on previously asymptomatic bone metastases in arm A was less than half that in arm B (14% and 30%, respectively), without, however, reaching statistical significance ($P = 0.18$). The global number of new painful sites was 7 in arm A and 22 in arm B, with a mean of 1.4 sites for patients in arm A and 2.2 sites for patients in arm B. Survival without new painful sites was significantly different in the 2 arms, at a median of 4 mo in arm A and 2 mo in arm B ($P = 0.04$) (Fig. 1B).

### Cytostatic Effect

Because 13 patients died too soon (<6 mo) to undergo follow-up scanning, bone disease changes were evaluable for only 30 of 35 patients in arm A and only 28 of 35 patients in arm B. Bone disease progressed during the 6 mo after

### TABLE 1
Baseline Variables in Patients Enrolled in Arm A

| Patient no. | Age (y) | Stratum | KS | PS | SS | PSA* | AP† |
|---|---|---|---|---|---|---|---|
| 1 | 62 | 1 | 60 | 3 | 3 | 292 | 2,556 |
| 2 | 61 | 2 | 50 | 3 | 4 | 110 | 83 |
| 3 | 65 | 1 | 70 | 3 | 2 | 847 | 392 |
| 4 | 71 | 2 | 50 | 3 | 4 | 359 | 8,527 |
| 5 | 67 | 1 | 90 | 1 | 3 | 140 | 689 |
| 6 | 63 | 1 | 80 | 3 | 2 | 31 | 427 |
| 7 | 69 | 1 | 70 | 3 | 3 | 42 | 1,580 |
| 8 | 58 | 1 | 80 | 2 | 4 | 45 | 1,481 |
| 9 | 76 | 1 | 60 | 3 | 3 | 352 | 1,888 |
| 10 | 65 | 2 | 50 | 3 | 3 | 732 | 416 |
| 11 | 78 | 2 | 50 | 3 | 3 | 20 | 688 |
| 12 | 78 | 2 | 50 | 2 | 3 | 541 | 3,739 |
| 13 | 64 | 1 | 70 | 3 | 2 | 256 | 141 |
| 14 | 68 | 2 | 50 | 3 | 3 | 1,435 | 1,150 |
| 15 | 69 | 2 | 40 | 4 | 4 | 52 | 1,255 |
| 16 | 70 | 1 | 70 | 3 | 2 | 517 | 822 |
| 17 | 67 | 1 | 70 | 3 | 3 | 259 | 191 |
| 18 | 80 | 1 | 80 | 2 | 2 | 532 | 1,405 |
| 19 | 75 | 1 | 70 | 3 | 4 | 182 | 2,879 |
| 20 | 76 | 2 | 40 | 3 | 2 | 504 | 788 |
| 21 | 69 | 1 | 70 | 2 | 3 | 275 | 1,070 |
| 22 | 72 | 1 | 70 | 3 | 3 | 148 | 1,445 |
| 23 | 59 | 1 | 80 | 3 | 2 | 134 | 768 |
| 24 | 71 | 1 | 70 | 2 | 3 | 645 | 1,777 |
| 25 | 73 | 1 | 50 | 3 | 2 | 250 | 750 |
| 26 | 72 | 2 | 50 | 3 | 2 | 450 | 844 |
| 27 | 79 | 2 | 90 | 3 | 3 | 568 | 1,900 |
| 28 | 73 | 1 | 80 | 4 | 2 | 836 | 690 |
| 29 | 77 | 1 | 100 | 1 | 1 | 369 | 320 |
| 30 | 66 | 1 | 90 | 2 | 2 | 79 | 980 |
| 31 | 66 | 1 | 80 | 3 | 2 | 617 | 940 |
| 32 | 71 | 1 | 90 | 4 | 2 | 329 | 1,100 |
| 33 | 57 | 1 | 80 | 3 | 3 | 482 | 2,500 |
| 34 | 62 | 1 | 90 | 1 | 3 | 81 | 1,300 |
| 35 | 62 | 1 | 90 | 3 | 1 | 360 | 1,380 |

KS = performance status score using Karnofsky Scale (score value, 0–100); PS = pain score using Wisconsin test (score value, 0–4); SS = scintigraphic score using criteria of Soloway et al. (*17*) (score value, 0–4).
*Reference range, 0–4 ng/mL.
†Reference range, 98–279 U/L.

### TABLE 2
Baseline Variables in Patients Enrolled in Arm B

| Patient no. | Age (y) | Stratum | KS | PS | SS | PSA* | AP† |
|---|---|---|---|---|---|---|---|
| 1 | 51 | 1 | 90 | 3 | 2 | 16 | 2,277 |
| 2 | 72 | 1 | 80 | 3 | 2 | 550 | 429 |
| 3 | 64 | 1 | 70 | 2 | 2 | 400 | 482 |
| 4 | 61 | 1 | 70 | 3 | 3 | 382 | 907 |
| 5 | 52 | 1 | 60 | 3 | 2 | 13 | 480 |
| 6 | 68 | 1 | 80 | 1 | 3 | 90 | 340 |
| 7 | 71 | 2 | 50 | 3 | 2 | 49 | 191 |
| 8 | 60 | 1 | 70 | 3 | 3 | 224 | 858 |
| 9 | 65 | 1 | 60 | 3 | 2 | 690 | 491 |
| 10 | 64 | 2 | 50 | 3 | 2 | 294 | 595 |
| 11 | 76 | 1 | 70 | 2 | 1 | 26 | 402 |
| 12 | 65 | 1 | 70 | 3 | 3 | 400 | 359 |
| 13 | 75 | 2 | 40 | 3 | 4 | 274 | 4,049 |
| 14 | 66 | 1 | 80 | 1 | 1 | 15 | 232 |
| 15 | 80 | 1 | 60 | 3 | 1 | 20 | 2,500 |
| 16 | 80 | 2 | 50 | 3 | 4 | 121 | 457 |
| 17 | 75 | 1 | 80 | 3 | 4 | 562 | 953 |
| 18 | 58 | 1 | 60 | 1 | 2 | 34 | 890 |
| 19 | 73 | 1 | 70 | 2 | 2 | 156 | 485 |
| 20 | 57 | 1 | 80 | 2 | 3 | 1,118 | 984 |
| 21 | 69 | 2 | 40 | 3 | 4 | 2,370 | 2,812 |
| 22 | 81 | 2 | 40 | 3 | 2 | 13 | 1,110 |
| 23 | 65 | 1 | 70 | 3 | 4 | 1,300 | 1,882 |
| 24 | 61 | 1 | 70 | 2 | 3 | 2,048 | 817 |
| 25 | 75 | 1 | 60 | 3 | 3 | 87 | 1,089 |
| 26 | 89 | 1 | 70 | 2 | 3 | 1,273 | 492 |
| 27 | 59 | 2 | 50 | 3 | 3 | 126 | 1,280 |
| 28 | 64 | 1 | 70 | 3 | 1 | 562 | 430 |
| 29 | 66 | 1 | 70 | 2 | 1 | 40 | 943 |
| 30 | 66 | 1 | 100 | 1 | 2 | 156 | 1,000 |
| 31 | 65 | 1 | 60 | 4 | 2 | 1,200 | 495 |
| 32 | 70 | 1 | 80 | 4 | 3 | 2,370 | 994 |
| 33 | 68 | 1 | 80 | 3 | 2 | 15 | 960 |
| 34 | 67 | 2 | 50 | 3 | 2 | 1,320 | 1,200 |
| 35 | 59 | 2 | 50 | 3 | 3 | 1,048 | 2,400 |

KS = performance status score using Karnofsky Scale (score value, 0–100); PS = pain score using Wisconsin test (score value, 0–4); SS = scintigraphic score using criteria of Soloway et al. (*17*) (score value, 0–4).
*Reference range, 0–4 ng/mL.
†Reference range, 98–279 U/L.

**TABLE 3**
Response Rates in Arms A and B

| Response | Arm A | Arm B | P |
|---|---|---|---|
| Complete | 28% (15%–46%) | 14% (5%–30%) | <0.25 |
| Partial | 46% (29%–63%) | 32% (16%–50%) | <0.3 |
| Minimal | 17% (6%–33%) | 17% (6%–33%) | |
| None | 9% (1%–23%) | 37% (21%–55%) | <0.01 |

Values in parentheses are 95% CIs.

therapy in 27% of patients in arm A and 64% of patients in arm B ($P = 0.01$). Bone disease was stable in 70% of patients in arm A and 36% of patients in arm B ($P = 0.02$). Bone disease showed a partial response in only 1 patient in arm A (Fig. 2).

Survival after therapy is illustrated in Figure 1 by Kaplan–Meier curves. To date, 59 of 70 patients that had been enrolled in the study have died (29 in arm A and 30 in arm B). Three patients in arm A died of causes unrelated to the tumor. Global survival after therapy ranges from 2 to 24 mo (median, 9 mo) in arm A and from 2 to 23 mo (median, 6 mo) in arm B ($P = 0.3$).

Changes in PSA and AP serum levels after therapy are illustrated in Figure 3.

**Marrow Toxicity**

Changes in platelets, leukocytes, and hemoglobin during follow-up are illustrated in Figure 4. No significant differences were observed in pretherapy platelet, leukocyte, or hemoglobin values between the 2 arms.

*Arm A.* WHO grade 1 platelet toxicity was apparent in only 1 patient, in whom a 26% decrease in the mean platelet count at 4 wk slowly returned to normal within 3 mo after therapy. WHO grade 1–2 leukocyte toxicity was observed in 8 patients, who had a transient 26% decrease in the mean leukocyte count at 4 wk. Fourteen patients showed hemoglobin toxicity, which was WHO grade 4 in 2; WHO grade 3 in 1, and WHO grade 1–2 in 11. The mean hemoglobin values decreased 10% from baseline levels at 4 wk after therapy and remained mildly impaired for 2 mo.

*Arm B.* WHO grade 1–2 platelet toxicity was apparent in only 2 patients, in whom a 22% decrease in the mean platelet count at 4 wk slowly returned to normal within 3 mo after therapy. WHO grade 2 leukocyte toxicity was observed in 2 patients, who had a 19% decrease in the mean leukocyte count at 6 wk. Thirteen patients showed hemoglobin toxicity, which was WHO grade 4 in 1, WHO grade 3 in 3, and WHO grade 1–2 in 9. The mean hemoglobin values decreased 6% from baseline levels at 2 mo after therapy and returned to normal within the following month.

**Other Results**

No side effects were clinically evident after cisplatin infusion. Ten patients (14%), 6 in arm A and 4 in arm B, experienced a mild, transient increase in pain, that is, a flare response, within 7 d after ${}^{89}$Sr injection. This response resolved within 24–48 h. No patient showed neurologic signs from nerve compression or renal function impairment. The Karnofsky performance score improved in 23 patients in arm A and 9 patients in arm B (66% and 26%, respectively; $P = 0.002$), remained the same in 6 patients in arm A and 11 patients in arm B (17% and 31%, respectively; $P = 0.2$), and worsened in 6 patients in arm A and 15 patients in arm B (17% and 43%, respectively; $P = 0.03$).
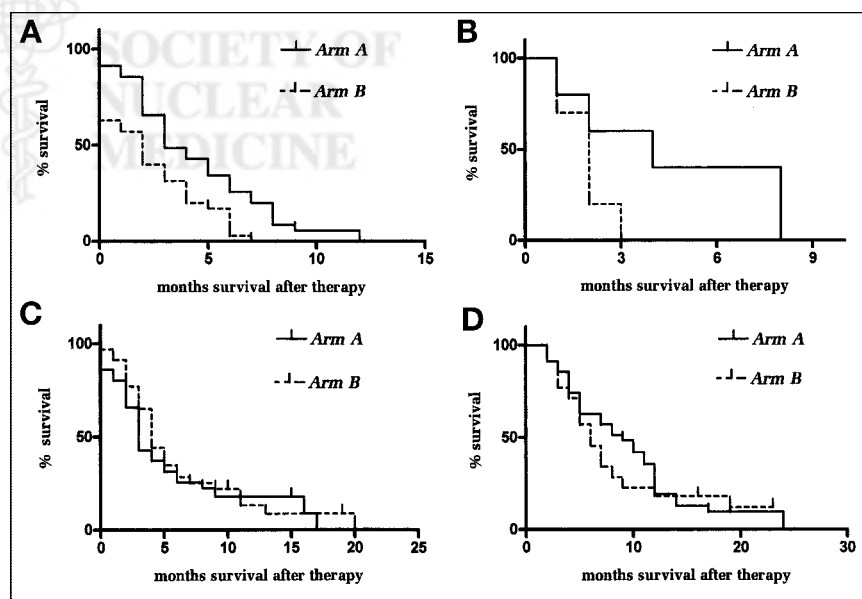


**FIGURE 1.** Kaplan–Meier curves illustrating survival times in the 2 arms: survival free of pain relapse (A), survival without new painful sites (B), survival after pain relapse (C), and global survival after therapy (D).
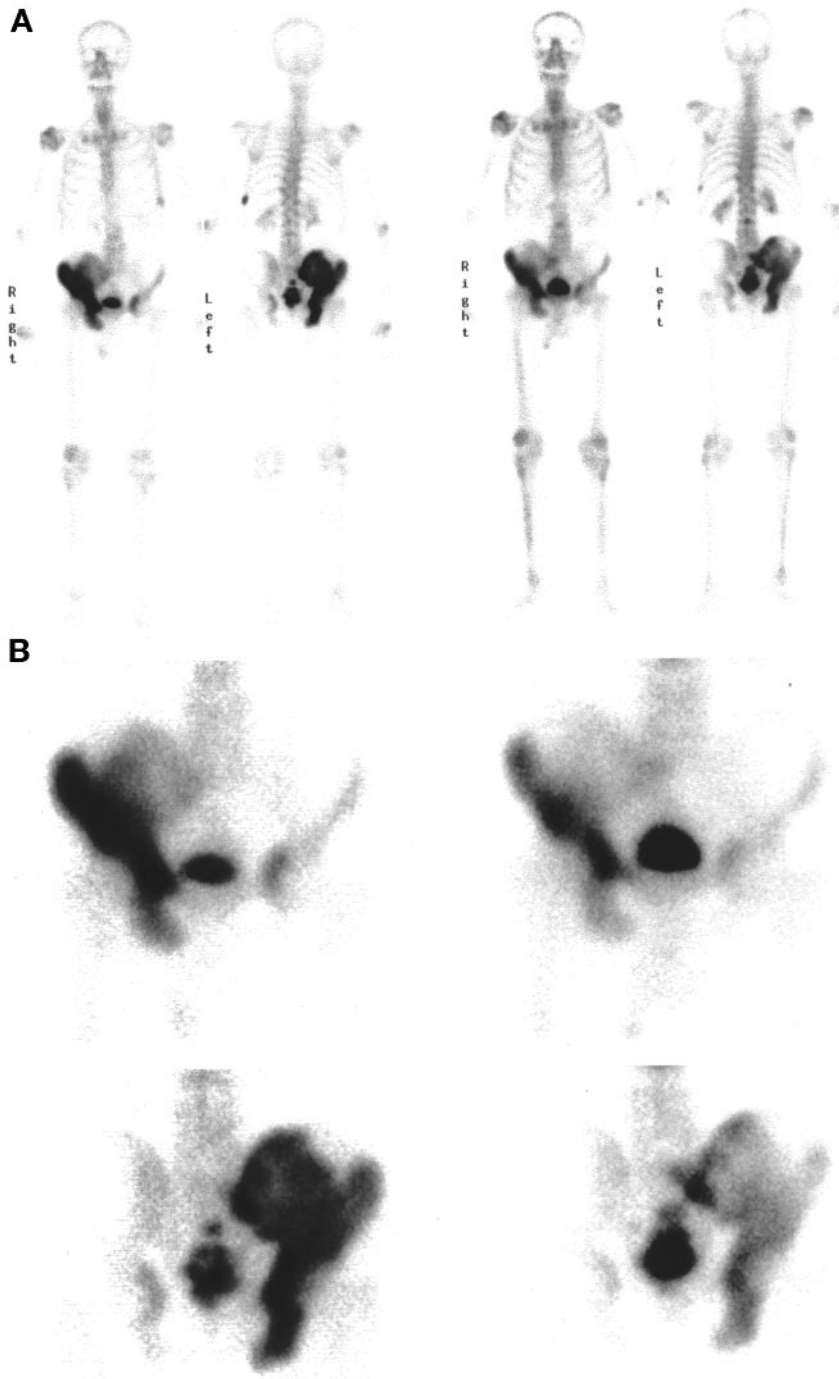
**FIGURE 2.** Pretherapy (left) and post-therapy (right) bone scintigraphy of patient 18 of arm A with bone disease and partial response. (A) Whole-body scan shows intense tracer uptake in right pelvis and in 1 left rib before therapy, with evident reduction in uptake after therapy. (B) Planar views of pelvis.

## DISCUSSION

[89]Sr has widely been used for more than 50 y to relieve pain caused by bone metastases, the first clinical use dating to 1942 (*21*). Although the clinical efficacy of ^{89}Sr is evident in 51%–96% of patients, only a small percentage of these patients experiences complete pain relief and only occasionally does objective evidence of tumor regression occur (*7–9,22–25*).

Cisplatin, a potent cytotoxic agent for a wide range of tumors, has radiosensitizing properties through several mechanisms when used at low doses (*26–28*). Preclinical data are available on the efficacy of cisplatin as a radiosensitizer in prostate cancer (*29–31*). The only available clinical experience with low-dose cisplatin plus β-emitter radionuclides is a preliminary report of Mertens et al. (*12*) on 18 patients with prostate carcinoma. That study, using a cisplatin schedule of 35 mg/m$^2$ infused over 2 d, 1 wk, and 4 wk after ^{89}Sr administration, showed good pain relief, mild toxicity, improvement in tracer uptake on posttreatment bone scans, and promising survival data. Unfortu-
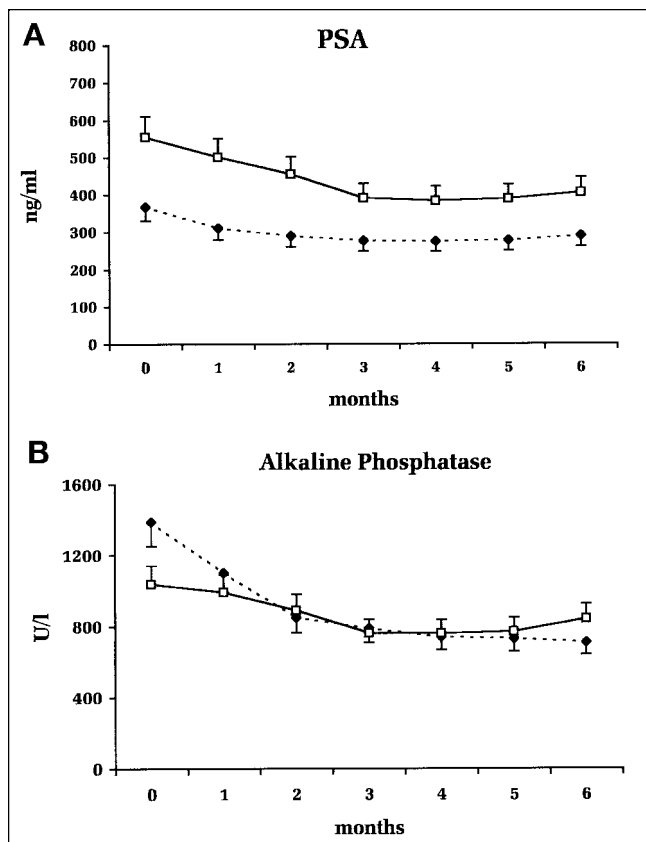
**FIGURE 3.** PSA (A) and AP (B) basal values and monthly values during 6 mo after therapy. Values are reported as mean $\pm$ SEM. $\blacklozenge$ = arm A; $\square$ = arm B.

low dose of cisplatin plus a standard dose of ^{89}Sr significantly increased ($P < 0.01$) the prevalence of overall pain relief. This increase stemmed entirely from effects on the complete and partial response rates, with a true doubling of patients who had complete pain relief (10 patients in arm A vs. 5 patients in arm B). The current results confirm the preliminary results of Mertens et al. (12). Unfortunately, data on the prevalence of pain palliation from most trials using ^{89}Sr alone are not comparable either with one another or with this study because of the small number of accrued or evaluable patients, the different or poorly defined criteria for evaluating responses, and the different inclusion criteria (7–9,22–25).
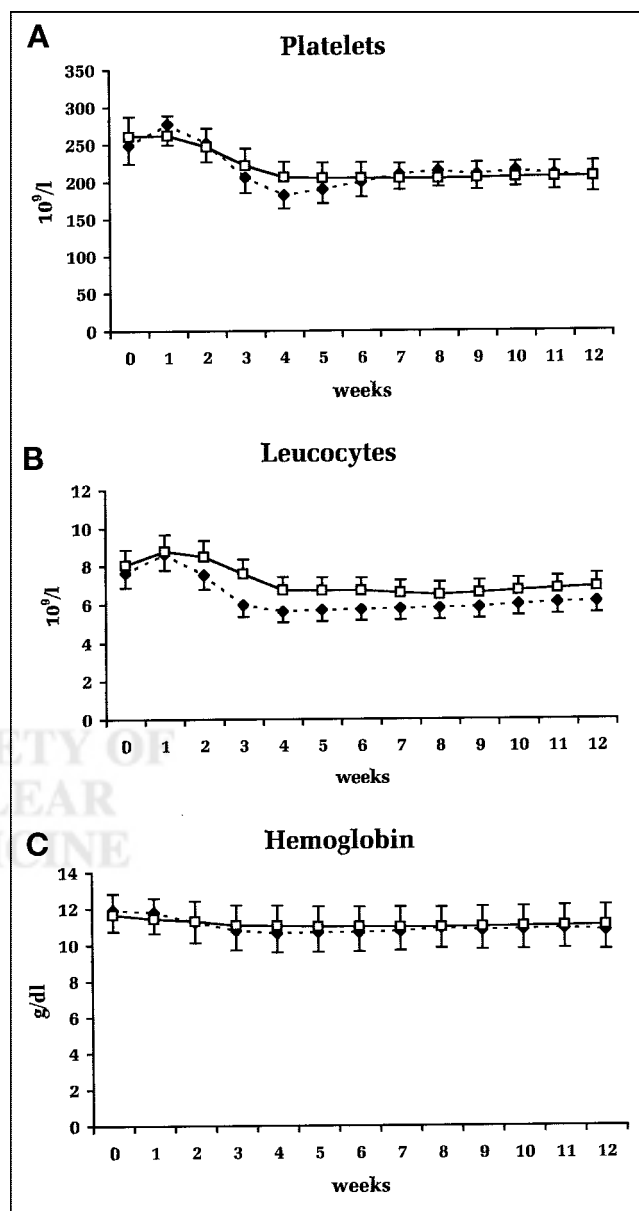
nately, the small sample size and single-arm design of the study made correlations between baseline variables and outcome difficult and did not support firm conclusions.

This study, being a randomized, controlled trial of a rational schedule of combined low-dose cisplatin and ^{89}Sr in a relatively large sample of patients with advanced prostate cancer, addresses the question in a more structured way. A cumulative cisplatin dosage of 50 mg/m$^2$ was chosen because doses of 20–100 mg/m$^2$ ensure tissual drug levels high enough for biochemistry-based enhancement of radiation sensitivity in mammalian cells, that is, 0.5–2 ppm (27,32–34), avoiding the myelotoxic effects of the usual chemotherapeutic doses (>100 mg/m$^2$).

The double administration of cisplatin (a few hours before and after 10 Gy ^{89}Sr irradiation) was chosen on the basis of previous experience (27,35,36) to maximally enhance radiation damage. In fact, an enhancement ratio of 1.23–1.45 after 10 Gy continuous low-dose-rate irradiation and concurrent cisplatin infusion was reported by Fu et al. (35,36) for murine models, whereas other studies have suggested that cisplatin could be given before radiation because cisplatin–DNA adducts can take some hours to reach and then remain for several days (27,29).

The schedule of this study effectively enhanced the effect of ^{89}Sr as addressed by all endpoints. In fact, the use of a



**FIGURE 4.** Platelet (A), leukocyte (B), and hemoglobin (C) basal values and weekly values during 3 mo after therapy. Values are reported as mean $\pm$ SEM. $\blacklozenge$ = arm A; $\square$ = arm B.

Pain palliation in this study was also significantly prolonged by the use of low-dose cisplatin plus $^{89}$Sr, with a doubling of the median duration of survival free of pain relapse (Fig. 1A). In addition, the relative risk of pain relapse in patients treated with $^{89}$Sr plus cisplatin was nearly half that in patients treated with $^{89}$Sr alone, with a hazard ratio (arm B to arm A) of 1.82 (95% CI, 1.40–4.45). These data fully agree with those of Mertens et al. (*12*), who reported a median duration of 4 mo for pain relief.

Both the number of patients presenting with new painful sites on previously asymptomatic metastases and the global number of new painful sites were consistently lower in arm A. In fact, in only 5 of 35 patients in arm A, versus 10 of 35 in arm B, did new painful sites develop on previously asymptomatic metastases, and onset was significantly later ($P = 0.04$) in arm A than in arm B. When the corresponding survival curves were analyzed (Fig. 1B), the hazard ratio for development of new painful sites for arm B was more than double that for arm A (ratio, 2.12). This finding could have important clinical significance well beyond the strictly palliative effect. In fact, only a small proportion of bone metastases become painful, and the factors that convert a painless lesion into a painful one are unknown (*37*). Pain onset may represent an increase in neoplastic bone invasion and be an early marker of bone disease progression.

Considering the second endpoint of the study, the cytostatic effect of using cisplatin plus $^{89}$Sr, the likelihood of such an effect on bone disease is confirmed by the changes in bone scan findings observed during follow-up. In fact, a significantly lower proportion of patients had disease progression in arm A (27%; 95% CI, 12%–45%) than in arm B (64%; 95% CI, 44%–81%). Objective measures of the response of bone disease to treatment with $^{89}$Sr alone have only occasionally been reported, with most patients exhibiting either stable disease (*24*) or progressive disease (*23*) on bone scans. In addition, comparison of trials is difficult because of differences in the extent of disease in the patients enrolled, when that extent has been adequately described (*38*). The response of osteoblastic bone metastases to treatment remains, however, difficult to quantify accurately (*39*). The National Prostate Cancer Group conducted a series of randomized phase II trials in the 1970s and established criteria for quantifying the response of measurable lesions (*18*). Our study reports for the first time the results of an objective evaluation of the response of bone disease to $^{89}$Sr, using strict, established criteria. However, consideration of other changes in scan findings, not strictly included in the established criteria, could also be worthwhile. In 2 arm A patients who were considered to have progressive disease because of the appearance of new metastases, previously evident metastases (in the pelvis and femur) disappeared, whereas 2 arm A patients who were classified as having stable disease showed a marked and diffuse decrease in tracer uptake in all metastatic sites. On the contrary, in no arm B patients did metastases previously detected on bone scans disappear, and only 1 patient showed a diffuse de-

crease in tracer uptake after therapy. A retarding effect of cisplatin on bone disease progression was also confirmed by changes in serum AP levels after therapy in the 2 arms. In fact, a significant decrease in AP levels was evident in arm A ($P < 0.001$), whereas only a marginally significant decrease was observed in arm B ($P = 0.06$). In addition, this effect was more prolonged in arm A (median, 4 mo) than in arm B (median, 2 mo).

This study did not show significant differences in global survival between the 2 arms, even though bone disease progressed more slowly in arm A. In fact, survival after pain relapse was quite similar in the 2 arms, with a median value of 4 mo in arm A and 3 mo in arm B ($P = 0.40$), whereas global survival after therapy increased in arm A without reaching statistical significance ($P = 0.30$) (Figs. 1C and 1D). Accordingly, PSA values had not significantly changed after therapy in either arm. The hazard ratio of arm B to arm A for global survival was 1.26, showing that the relative risk of dying was moderately higher in arm B than in arm A. Further investigation of these results in a larger number of patients could be worthwhile to firmly rule out the chance of a β-error. Another question for future studies to address is whether enrolling patients with less advanced cancer or using more aggressive cisplatin schedules may affect global survival.

Marrow toxicity was only slightly increased by the addition of cisplatin, without significant differences between the 2 arms.

## CONCLUSION

A low dose of cisplatin enhances the effect of a standard dose of $^{89}$Sr without significantly increasing marrow toxicity. Combined treatment not only significantly improves pain palliation, increasing the response rate and prolonging pain-free survival, but also has a cytostatic effect on bone disease, decreasing the risk of progression.

## REFERENCES

1. Payne R. Pain management in the patient with prostate cancer. *Cancer.* 1993; 71(suppl 3):1131–1137.
2. Twycross RG, Fairfield S. Pain in far-advanced cancer. *Pain.* 1982;14:303–310.
3. Fitzpatrick PJ, Rider WD. Half body radiotherapy. *Int J Radiat Oncol Biol Phys.* 1976;1:197–207.
4. Eisenberger MA. Chemotherapy for prostate carcinoma. *Natl Cancer Inst Monogr.* 1988;7:151–163.
5. Krishnamurthy GT, Krishnamurthy S. Radionuclides for metastatic bone pain palliation: a need for rational re-evaluation in the new millennium. *J Nucl Med.* 2000;41:688–691.
6. McEwan AJ. Unsealed source therapy of painful bone metastases: an update. *Semin Nucl Med.* 1997;27:165–182.
7. Silberstein EB, Williams C. Strontium-89 therapy for the pain of osseous metastases. *J Nucl Med.* 1985;26:345–348.
8. Robinson RG, Preston DF, Schiefelbein M, Baxter KG. Strontium-89 therapy for the palliation of pain due to osseous metastases. *JAMA.* 1995;274:420–424.

9. Kloiber R, Molnar CP, Barnes M. Sr-89 therapy for metastatic bone disease: scintigraphic and radiographic follow-up. *Radiology.* 1987;163:719–723.

10. Blake GM, Zivanovic MA, McEwan AJ, Batty VB, Ackery DM. [89]Sr radionuclide therapy: dosimetry and haematological toxicity in two patients with metastasising prostatic carcinoma. *Eur J Nucl Med.* 1987;13:41–46.

11. Blake GM, Zivanovic MA, Blaquiere RM, Fine DR, McEwan AJ, Ackery DM. Strontium-89 therapy: measurement of adsorbed dose to skeletal metastases. *J Nucl Med.* 1988;29:549–557.

12. Mertens WC, Porter AT, Reid RH, Powe JE. Strontium-89 and low-dose infusion cisplatin for patients with hormone refractory prostate carcinoma metastatic to bone: a preliminary report. *J Nucl Med.* 1992;33:1437–1443.

13. Fowler JF. Radiobiological aspects of low dose rates in radioimmunotherapy. *Int J Radiat Oncol Biol Phys.* 1990;18:1261–1269.

14. Sciuto R, Maini CL, Tofani A, Fiumara C, Scelsa MG, Broccatelli M. Radiosensitization with low-dose carboplatin enhances pain palliation in radioisotope therapy with strontium-89. *Nucl Med Commun.* 1996;17:799–804.

15. Sciuto R, Festa A, Tofani A, et al. Platinum compounds as radiosensitizers in strontium-89 metabolic radiotherapy. *Clin Ter.* 1998;149:43–47.

16. Sciuto R, Tofani A, Festa A, Giannarelli D, Pasqualoni R, Maini CL. Short- and long-term effects of [186]Re-1,1-hydroxyethilidene diphosphonate in the treatment of painful bone metastases. *J Nucl Med.* 2000;41:647–654.

17. Soloway MS, Hardeman SW, Hickey D, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer.* 1988;61:195–202.

18. Labrie F, Dupont A, Giguere M, et al. Important prognostic value of standardized objective criteria of response in stage D2 prostatic carcinoma. *Eur J Cancer Clin Oncol.* 1988;24:1869–1878.

19. World Health Organization. *WHO Handbook for Reporting Results for Cancer Treatment.* Geneva, Switzerland: World Health Organization; 1979. WHO offset publication 48.

20. Motulsky H. *Intuitive Biostatistics.* New York, NY: Oxford University; 1995: 113–117.

21. Pecher C. Biological investigation with radioactive calcium and strontium: preliminary report on the use of radioactive strontium in the treatment of metastatic bone cancer. *Univ Calif Publ Pharmacol.* 1942;2:117–149.

22. Bolger JJ, Dearnaley DP, Kirk D, et al., for the UK Metastron Investigators Group. Strontium-89 (Metastron) versus external beam radiotherapy in patients with painful bone metastases secondary to prostatic cancer: preliminary report of a multicenter trial. *Semin Oncol.* 1993;20(suppl 2):32–33.

23. Tennvall J, Darte L, Lundgren R, el Hassan AM. Palliation of multiple bone metastases from prostatic carcinoma with strontium-89. *Acta Oncol.* 1988;27:365–369.

24. Laing AH, Ackery DM, Bayly RJ, et al. Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *Br J Radiol.* 1991;64:816–822.

25. Porter AT, Mertens WC. Strontium-89 in the treatment of metastatic prostate cancer. *Can J Oncol.* 1991;1:11–18.

26. Dewit L. Combined treatment of radiation and cisdiamminedichloroplatinum (II): a review of experimental and clinical data. *Int J Radiat Oncol Biol Phys.* 1987;13:403–426.

27. Begg AC. Cisplatin and radiation: interaction probabilities and therapeutic possibilities. *Int J Radiat Oncol Biol Phys.* 1990;19:1183–1188.

28. Coughlin CT, Richmond RC. Biologic and clinical developments of cisplatin combined with radiation: concepts, utility, projections for new trials, and the emergence of carboplatin. *Semin Oncol.* 1989;16(suppl 6):31–43.

29. Coughlin CT, Richmond RC, Page RL. Platinum drug delivery and radiation for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys.* 1994;28:1029–1038.

30. Geldof AA, Slotman BJ. Radiosensitizing effect of cisplatin in prostate cancer lines. *Cancer Lett.* 1996;101:233–239.

31. Geldof AA, de Rooij L, Versteegh RT, Newling DW, Teule GJ. Combination [186]Re-HEDP and cisplatin supra-additive treatment effects in prostate cancer cells. *J Nucl Med.* 1999;40:667–671.

32. Coughlin CT, Richmond RC. Platinum based combined modality approach for locally advanced head and neck carcinoma. *Int J Radiat Oncol Biol Phys.* 1985;11:915–919.

33. Mattox DE, Sternson LA, Von Hoff DD, et al. Tumor concentration of platinum in patients with head and neck cancer. *Arch Otolaryngol.* 1983;91:271–275.

34. Stewart DJ, Leavens M, Maor M, et al. Human central nervous system distribution of *cis*-diamminedichloroplatinum and use as radiosensitizer in malignant brain tumors. *Cancer Res.* 1982;42:2474–2479.

35. Fu KK, Rayner PA, Lam KN. Modifications of the effects of continuous low dose rate irradiation by concurrent chemotherapy infusion. *Int J Radiat Oncol Biol Phys.* 1984;10:1473–1478.

36. Fu KK, Lam KN, Rayner PA. Effects of continuous low-dose irradiation and concurrent infusion of mitomycin, cisplatin and 5-fluorouracil on three mouse tumors. *Endocurie Hypertherm Oncol.* 1986;2:157–162.

37. Portenoy RK, Lesage P. Management of cancer pain. *Lancet.* 1999;353:1695–1700.

38. Robinson RG, Spicer JA, Preston DF, Wegst AV, Martin NL. Treatment of metastatic bone pain with strontium-89. *Int J Rad Appl Instrum B.* 1987;14:219–222.

39. Sabbatini P, Larson SM, Kremer A, et al. Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. *J Clin Oncol.* 1999;17:948–957.