Samarium-153-EDTMP in Bone Metastases of Hormone Refractory Prostate Carcinoma: A Phase I/II Trial

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Samarium-153-ethylenediaminetetramethylene phosphonic acid (EDTMP), a bone-seeking radiopharmaceutical, was given to prostate cancer patients in a dose escalation protocol for pain palliation to determine the maximally tolerated dose. Fifty-two patients with hormone refractory prostate cancer with bony metastases were treated with doses beginning at 0.5 mCi/kg (18.5 MBq/kg), escalating in 0.5-mCi (18.5 MBq) increments to 3.0 mCi/kg (111 MBq/kg). Pain response after treatment was assessed as well as hematologic and serum chemistry parameters. Pain palliation with a mean duration of 2.6 mo was present in 74% of the patients. Toxicity was exclusively hematologic at the highest dose levels. No infectious or bleeding complications occurred, with 45 of the 52 (86%) patients demonstrating complete hematologic recovery. Patients receiving higher doses had significantly greater reductions in serum prostate specific antigen and serum prostatic acid phosphatase levels. The patients receiving greater doses also showed a trend toward improved survival.

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Primary treatment for advanced prostate carcinoma is hormonal therapy. However, once patients fail initial hormonal therapy, the outlook is poor with a median survival of about 9 mo (*1*). In disseminated prostate cancer, the dominant pattern is widespread osteoblastic bony metastases and many patients die without other major organ involvement as a consequence of immobilization and inanition. The major clinical problem is pain relief and optimal radiation therapy is often compromised by widespread nature of skeletal metastases. The use of chemotherapy in this setting is controversial as there is little evidence that either single agents or combinations results in meaningful prolongation of survival (*2*).

Although there are many radioisotopes which have been proposed as therapeutic agents in the treatment of carcinoma (*3–7*), ^{153}Sm has several physical characteristics which suggest usefulness in treatment of pain from metastatic bone lesions. Samarium-153 has 810 (20%), 710 (50%) and 640 (30%) keV beta particle emissions (average = 290 keV) which penetrate tissue over a relatively short distance (3 mm) and are suitable for therapy. Gamma emission at 103 keV (29.8%) which is ideal for standard scintigraphic scanning, allows specific localization of metastases. The short half-life (46.27 hr) allows for efficient handling and the possibility of fractionated dosing. Samarium-153 has been chelated to ethylenediaminetetramethylene phosphonic acid (EDTMP) producing a bone-seeking diphosphonate complex that is chemically and biologically stable, localizing in bone preferentially and concentrating in skeletal metastases (*5,6,8*). Toxicity results in the Phase I dose-seeking portion of the trial are presented in this report followed by the Phase II observations of pain palliation and tumor response.

MATERIALS AND METHODS

Patient Staging and Eligibility

All patients had bone dominant prostate carcinoma refractory to hormone treatment. Although this was not a randomized study, there were no significant differences in either the extent of bone metastases on bone scans or the pretreatment hemoglobin, alkaline phosphatase, LDH or performance status between the patient dose groups. Criteria for entry into the trial was a positive ^{99m}Tc-MDP bone scan consistent with bony metastases. Staging evaluation included a complete history and physical examination. Laboratory studies included a complete blood count with differential and platelet count, prothrombin and partial thromboplastin times, BUN, creatinine, calcium, phosphate, SGOT, SGPT, LDH, alkaline phosphatase, bilirubin, total protein, albumin, uric acid, prostatic acid phosphatase (PAP), prostate specific antigen (PSA) and urinalysis. Patients had a ^{99m}Tc-MDP total body bone scan with determination of 24-hr total body radioactivity retention and estimation of tumor-to-normal bone uptake ratios. Radiographs of sites of major bony involvement detected on bone scans and chest x-rays were obtained. Patients with soft tissue metastases were not eligible. Study eligibility criteria also included a Southwest

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TABLE 1
Patient Characteristics

Age	
Median	71 yr
Range	50–86 yr
Performance status	
SWOG 0–1	39 (75%)
SWOG 2–3	13 (25%)
Previous chemotherapy	8 (15%)
Previous radiation therapy	
Primary to prostate	20 (38%)
Metastatic bony lesions	31 (60%)

Oncology Group performance status of 3 or better (capable of limited self-care) and adequate hematologic function with a neutrophil count ≥2,000/mm^3, hemoglobin ≥10.0 g/dl and platelet count ≥100,000/mm^3. All patients had serum creatinine <1.5 mg/dl, BUN <30 mg/dl and total bilirubin <1.5 mg/dl. Patients had received no more than one regimen of chemotherapy prior to treatment. Previous radiation or chemotherapy must have been completed 4 wk or more before treatment and a second line hormonal therapy must have been started 6 wk or more prior to study entry. Patients who had received maximum tolerable radiation to the spinal cord, pathologic bone fracture, spinal cord compression, unstable spine or imminent long bone fracture by plain film examination were ineligible. After a detailed explanation, all patients signed a written informed consent for treatment. The study protocol and consent were approved by the University of Washington Human Subjects Review and Radiation Safety Committees.

Treatment

Samarium-153-Cl was obtained from the University of Missouri Research Reactor. This material was complexed to the bone avid chelant, EDTMP, using a lyophilized kit (*6*). Fifty-two patients were treated in this Phase I/II study of ^{153}Sm-EDTMP. Their characteristics are outlined in Table 1. The first four patients received 1.0 mCi/kg (37 MBq/kg) of ^{153}Sm-EDTMP. The dose was escalated in successive groups of four patients by increments of 0.5 mCi/kg (18.5 MBq/kg) until a defined level of toxicity was achieved which was defined as the maximum tolerated dose (MTD) for this trial. This was grade III or greater toxicity (SWOG criteria, Table 2) attributable to ^{153}Sm-EDTMP observed in two of four patients at a single dose level. After completion of the dose escalation phase, an additional 16 patients were studied at the 2.5 and 1.0 mCi/kg (93 and 37 MBq/kg) dose level to further define differences in toxicities and response rates at high and low dose.

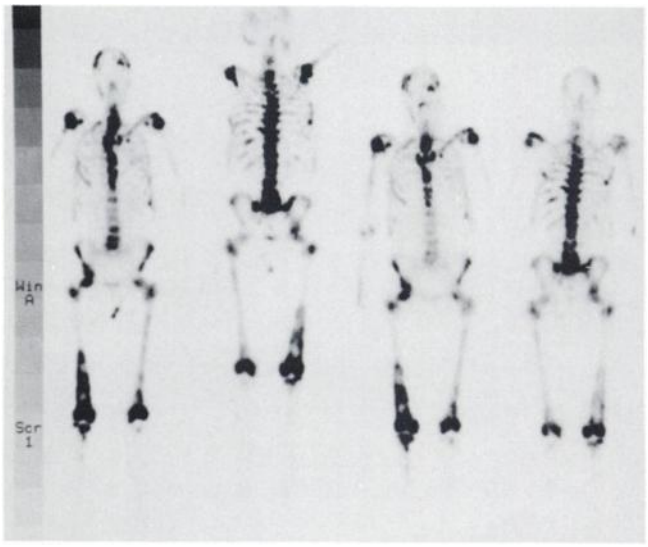

FIGURE 1. Anterior and posterior ^{99m}Tc-MDP radionuclide bone scans (left) of Patient 15 who received 2.5 mCi/kg ^{153}Sm-EDTMP compared with anterior and posterior ^{153}Sm-EDTMP scans (right) obtained 48 hr after administration.

All patients were treated in single rooms with appropriate shielding to minimize exposure of health care personnel. The ^{153}Sm-EDTMP was infused over 30 min by an infusion pump through a separate intravenous line used solely for this purpose. Calcium gluconate was available in the room for emergency use. All patients began hydration with 1000 ml dextrose 5% normal saline with 30 mEq of KCl at a rate of 2000 ml/m^2/24 hr, 6–8 hr prior to the infusion of ^{153}Sm-EDTMP and continued for an additional 12 hr. Bladder irrigation with 1000 ml urological saline plus 2 ml GU irrigant (neomycin plus polymyxin B) was done at a flow rate of 1000 ml/hr via a three-way Foley catheter beginning 1 hr prior to the infusion of ^{153}Sm-EDTMP and continuing for 8 hr after the infusion. All patients were imaged under a standard nuclear medicine gamma camera to assess the localization of the radiopharmaceutical 24–48 hr after receiving ^{153}Sm-EDTMP (Fig. 1). Patients were discharged from the hospital when the total body activity was <30 mCi.

TABLE 2
Hematologic Toxicity

Dose (mCi/kg)	Dose range (mCi)	Neutrophils*		Platelets†		Mean fall Hgb (Range)
		Grade II	Grades III/IV	Grade II	Grades III/IV	
1.0	51–105	1/20	2/20	3/20	2/20	1.6 (+0.2–3.0)
1.5	138–176	2/4	1/4	1/4	0/4	2.2 (1.0–3.0)
2.0	147–220	1/4	1/4	0/4	0/4	2.2 (0.6–2.2)
2.5	149–299	10/20	7/20	5/20	8/20	2.8 (0.6–4.3)
3.0	224–294	2/4	2/4	1/4	1/4	3.2 (1.3–5.1)

*Neutrophils: Grade II toxicity = 1,000 to 1,500/mm^3; Grade III toxicity = 500 to 900/mm^3; and Grade IV toxicity = less than 500/mm^3.
†Platelets: Grade II toxicity = 50,000 to 75,000/mm^3; Grade III toxicity = 25,000 to 49,000/mm^3; and Grade IV toxicity = less than 25,000/mm^3.
Hgb = hemoglobin (g/dl).

Toxicity Evaluation

Patients had a complete blood count with absolute neutrophil count and platelet count every other day until full hematologic recovery occurred and then monthly while on the study. Electrolytes, BUN, creatinine, calcium, phosphate, SGOT, SGPT, alkaline phosphatase, bilirubin, total protein, albumin, uric acid, PT and PTT were done weekly for 4 wk and then monthly. PAP and PSA levels were obtained on days 15 and 28 and on a monthly basis thereafter. Urinalysis was performed at the end of the first week and month, and then on a monthly basis. Radiographs of sentinel lesions were obtained monthly. Patients had a post-treatment radionuclide bone scan with 24-hr total body retention determination and tumor-to-normal bone ratios 4 wk after treatment and then every 2 mo following treatment. Criteria for hematologic toxicity are defined as indicated in Table 2.

Pain Response Assessment

Physicians rated pain response on a scale of −2 (considerable deterioration) to +2 (considerable improvement) and performance status weekly for 4 wk and then monthly until pain progression occurred. Patients kept a daily pain diary in which they assessed their general discomfort level on a scale of 1 (no pain) to 5 (pain severe, all activities restricted) and their sleep pattern on a scale from 1 (slept all night without medications) to 5 (awake most of the night secondary to pain) on a daily basis. Additionally they indicated specific sites of pain and rated these individual sites on a scale of 0 (no pain) to 10 (worst possible pain), with the ratings rounded to the nearest half point. The amount and timing of both nonopioid and opioid pain medications taken in a 24-hr period were recorded in a daily log. All opioids were converted to morphine equivalents in order to assess changes in pain medications (*9*). These diaries were reviewed weekly for 4 wk and then monthly as long as the patient remained in the study.

Because diary forms were open-ended, they imposed no structure on how patients described their pain sites. Given the uncertainty inherent in open-ended classifications, pain sites not mentioned on a particular day were not assumed to be actually zero; the patient could report pain from a given site elsewhere under an overlapping or alternative label. Even apart from measurement uncertainty, it may be unreasonable to expect to track pain coherently by site in this population because of the complex patterns of secondary and referred pains even when the original stimulus is a localized lesion. A simple summation of all pain scores is inconsistent with the knowledge of pain mechanisms as the central nervous system does not summate pains linearly. Moreover, it would allow total pain to be arbitrarily higher than the upper anchors of the individual pain scales, which already correspond to maximum pain. Therefore, a hyperbolic transformation of the visual analog scales that approaches an asymptote of 10, the scale maximum, was employed when pains combine from different sites in order to determine an overall pain score. For two pain sites, the transformation is $c = (a + b)/(1 + ab/10^2)$, where a and b are the two pains to be summed and c is the result (*10*). For more than two pains, the transformation is applied recursively. The effects of multiple pains combine nearly linearly when the pains are few and small, but behave asymptotically as their number or magnitude increases. In our study, the chi-squared test with Yates' correction was used for comparison of proportions where appropriate. Comparison of means was by the t-test and all comparisons were two-sided for significance.

RESULTS

Toxicity

All 52 patients were evaluable for toxicity. As two patients at the 2.5-mCi/kg (93 MBq/kg) dose level and two of four at the 3.0-mCi/kg (111 MBq/kg) level developed Grade III hematologic toxicity, the maximum tolerated dose in this trial was determined to be 2.5 mCi/kg. Because only four patients were treated at each dose level, an additional 16 patients were treated at a low (1.0 mCi/kg) and a high (2.5 mCi/kg) dose level to further define the difference in toxicity between these doses. The only toxicity observed was hematologic (Table 2). Increased dose levels showed increased marrow suppression. The mean nadir neutrophil count was 2,100/mm^3 in the 1.0-mCi/kg dose level compared to 1,000/mm^3 in the patients who received 2.5 mCi/kg ($p < 0.001$). No patient experienced a febrile illness, documented infection or an episode of hemorrhage. The mean nadir platelet count at the 1.0-mCi/kg dose level was 132,000/mm^3 compared to 65,000/mm^3 in the 2.5-mCi/kg group ($p < 0.001$). Anemia was more pronounced in patients at the higher dose levels: there was a significantly greater mean decrease in hemoglobin ($p < 0.01$) in the 2.5 mCi/kg dose level (2.8 g/dl) compared to the 1.0-mCi/kg dose level (1.6 g/dl). The median neutrophil nadir was Day 21 with a median time of 44 days to recovery of 2,000/mm^3. The median platelet nadir was Day 26 with a median time of 37 days to recovery of 100,000/mm^3. There was no trend for a more prolonged recovery time at the higher dose levels. Hematologic recovery of both neutrophils and platelets occurred in 45 of 52 patients (87%). Of the seven patients who did not show full hematologic recovery, five either had marrow replacement with prostatic carcinoma, or radiation therapy for progressive disease after treatment with ^{153}Sm-EDTMP. There was no evidence of radiation cystitis, despite the fact that 20 men (38%) had received radiation therapy to the pelvis as primary treatment for prostate carcinoma and an additional four patients (8%) had received palliative irradiation to the pelvis.

Treatment Response

Forty-six of the 52 men (88%) were evaluable for pain response. Overall pain response to treatment with ^{153}Sm-EDTMP was 76%. Pain responses occurred at all dose levels. Table 3 details the percent of all patients responding at 4 wk by physician assessment of pain and performance status as well as by analysis of patient diaries for changes in overall discomfort, hyperbolic pain transformation based on self-report scale ratings of specific pain sites, sleep patterns, and both opioid and nonopioid pain medications (Figs. 2, 3 and 4). Twelve of the 38 (32%) men on opioid medications prior to treatment were able to discontinue these medications 1 mo after therapy. There was a significant difference favoring the 2.5-mCi/kg dose level from baseline to Week 1 in patient self-report of pain ($p = 0.024$). By multivariate analysis, the 2.5-mCi/kg group exhibited greater improvement in opioid use over the entire study period ($p = 0.015$) than the 1.0 mCi/kg group. There

TABLE 3
Response at Four Weeks

	Overall	1.0 mCi/kg	2.5 mCi/kg
Physician assessment			
Pain response	34/46 (76%)	14/20 (70%)	12/15 (80%)
Improvement in PS	9/46 (20%)	3/20 (15%)	3/15 (20%)
Daily diary analysis			
Pain response (visual analog scale)	30/45 (67%)	11/20 (55%)	9/14 (64%)
Improvement in discomfort	36/45 (80%)	15/20 (75%)	13/14 (93%)
Improvement in sleep patterns	23/45 (45%)	11/20 (51%)	6/14 (43%)
Decrease in nonopioid drugs	16/45 (36%)	4/20 (20%)	5/14 (35%)
Decrease in opioid drugs	26/45 (58%)	10/20 (50%)	9/14 (64%)

was no apparent correlation between the number of bone metastases or the percent of ^{153}Sm-EDTMP retention and the pain response. In responders, pain relief occurred promptly, within 7 to 14 days of treatment. Six men (12%) had pain flares after treatment. Of the 16 men who had developed recurrent pain in a previously radiated site, 12 had pain improvement in that site after ^{153}Sm-EDTMP. All men had progressive pain with a median duration of palliation of 2.6 mo (range 1–8.8 mo) after treatment.

At 1 mo, 17 (33%) and 32 (62%) of the 52 patients had decreases (>25%) in the PSA and PAP levels, respectively. At 4 wk, PSA decreased in 2 of 20 (10%) treated at 1.0 mCi/kg and 10 of 20 (50%) treated at 2.5 mCi/kg, with a persistent difference evident at 8 wk (7% versus 42%, respectively). Decreases in PAP demonstrated similar differences. Kolmogorow-Smirnow tests of change distributions indicated that patients in the 2.5 mCi/kg dose level experienced significantly greater decreases than those in the 1.0 mCi/kg dose level at 4 wk on both PSA ($p = 0.035$, two-tailed) and PAP ($p = 0.001$, two-tailed). Changes in pain response did not correlate with changes in PSA and PAP (Table 3).

On bone scan appearance, this group of men had extensive disease with 38 (73%) having greater than 20 separate areas of abnormal uptake or a superscan. At 1 mo, 36 of the 50 (72%) patients who had bone scans were stable to improved, and 23 of the 30 patients (72%) who achieved a pain response by self-assessment had stable or improved ^{99m}Tc-MDP bone scan appearance. Seven of the 30 pain responders had progressive disease on bone scan at 1 mo, as well as six of the 13 nonresponders. There was no evidence of bone healing on standard radiographs after treatment and median survival of the entire group was 8 mo after treatment. As shown in Figure 5, the survival of the patients who received 2.5 mCi/kg of ^{153}Sm-EDTMP is significantly longer ($p = 0.03$) than that of those who received 1.0 mCi/kg (median 9 versus 6 mo).

DISCUSSION

Radiation therapy is an integral component in the treatment of osseous metastases. A multi-institutional trial by the Radiation Therapy Oncology Group investigating various dose fractionation schedules has shown that standard photon radiation therapy produces pain relief in 80%–85% of patients with bony metastases from a variety of malignancies (*11*). Complete responses occur in about 50% of patients with a 3-mo median duration of response with this treatment modality. Radiation therapy however, is limited to treatment of discrete disease sites. Patients with hormone refractory prostate cancer experiencing pain in multiple disease sites cannot be treated effectively with this type of radiation delivery. Over the years there has been substantial interest in the development of targeted therapy

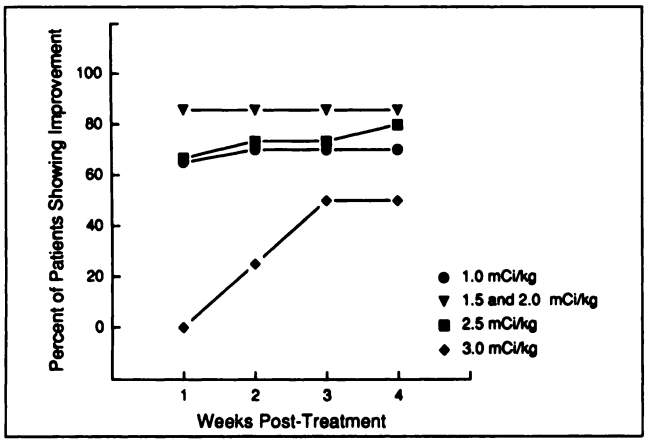

FIGURE 2. Physician's assessment of pain improvement by physician at Weeks 1–4 by ^{153}Sm-EDMTP dose level.

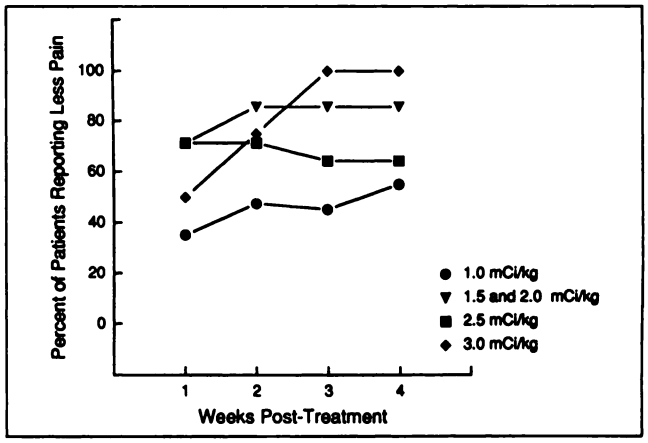

FIGURE 3. Improvement from baseline in hyperbolically transformed self-reported pain scores as reported in patient diaries at Weeks 1–4 by ^{153}Sm-EDMTP dose level.

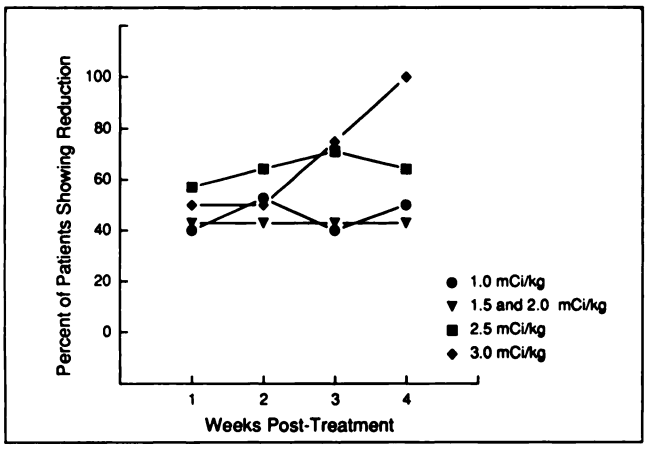

FIGURE 4. Reduction in baseline opioid pain medications from patient diaries at Weeks 1–4 by ^{153}Sm-EDMTP dose level.

for the treatment of cancer because of the widespread extent of bony disease in cancer patients. One approach is the use of small molecules which have a natural affinity for a particular organ. The fact that diphosphonates bind to metabolically active bone has been exploited with ^{99m}Tc chelated to MDP as the agent commonly used in radionuclide bone scans. Quantitative biodistribution studies of ^{153}Sm chelated to the multidentate phosphonate, EDTMP, in normal dogs showed that bone accumulates 84 times more activity than the kidney, with all other tissues having even higher ratios (*12*). In humans, ^{153}Sm-EDTMP has been shown to be a stable compound, with a similar biodistribution profile and rapid blood clearance with less than 5% of the complex remaining in blood at 4 hr postinjection (*8*). The scintigraphic images are similar to ^{99m}Tc-MDP, although the uptake in purely lytic lesions is uncertain (*5,6,13,14*).

It is apparent from the toxicity data presented that the maximum tolerated, and optimal dose of ^{153}Sm-EDTMP for pain palliation has not been defined. There was more myelosuppression at the higher dose levels but other factors such as the degree of marrow replacement by tumor, extent of bony metastases and previous radiation therapy, could account for some differences in the toxicity. Appelbaum et al. reported a dose escalation trial in dogs where a dose of 30 mCi/kg of ^{153}Sm-EDTMP was tolerated (*12*). At doses of 10.0 mCi/kg and above, there was no significant difference in the degree of marrow aplasia or the time to recovery. Even at the highest dose level, marrow ablation was not permanent and all dogs demonstrated full hematologic recovery (*12*). Autoradiographs demonstrated that the ^{153}Sm-EDTMP deposited preferentially in the trabecular marrow, but spared the midshaft of the long bones which evidenced hematologic recovery while the usual locations of red marrow were still aplastic (*12*). This preclinical therapy model result suggests that toxicity in patients may demonstrate a "plateau" phase in toxicity at much higher doses than was observed in this trial.

The canine model also suggests that the half-life of ^{153}Sm-EDTMP is short enough that it should be feasible to deliver multiple doses, analogous to fractionated dosing schedules for standard external beam irradiation. Turner et al. recently reported 23 patients with bone dominant metastatic carcinoma treated with a single dose of ^{153}Sm-EDTMP, of whom 15 went on to receive a second dose (*15*). The amount of ^{153}Sm-EDTMP administered was calculated to deliver 2,000 cGy absorbed dose to the bone marrow. Median duration of pain control (24 wk) and survival (9 mo) was greater in the patients who received two doses than those who received a single dose of ^{153}Sm-EDTMP. Thirteen of those patients (87%) achieved pain control and additional toxicity was confined to anemia after the second dose.

Because improvement of pain is difficult to quantitate, we used serial assessments by both physicians and the patients via a daily pain diary of multiple parameters to determine response in this study. The trends in all parameters showed that patients derived demonstrable benefit from treatment with ^{153}Sm-EDTMP. While more than 50% of patients had improvement in their opioid use, 32% who required opioid medications prior to administration of ^{153}Sm-EDTMP were able to discontinue these medications by one month. Forty-five percent of patients reported improvement in their sleep patterns and more than 60% of both patients and physicians reported improvement in global pain and discomfort in overall pain from all sites. The median duration of pain response was 2.6 mo. Similarly, Turner et al. treated 34 evaluable patients with bone metastases from a variety of malignancies with ^{153}Sm-EDTMP, producing pain relief in 65% of patients for periods ranging from 4 to 35 wk (*13*). The doses in that study were substantially smaller than in the trial we report here, ranging from 0.28 to 0.97 mCi/kg. However, the reported myelosuppression at doses <1.0 mCi/kg was similar to that reported here. Another dose escalation study in humans was done by Faranghi et al. who treated 22 patients with a variety of solid tumors with doses of ^{153}Sm-EDTMP up to 1.0 mCi/kg (*16,17*). They reported a similar pain palliation response rate and only mild hematologic toxicity.

The difficulty of assessing objective tumor responses in metastatic prostate carcinoma is notorious. We used serum

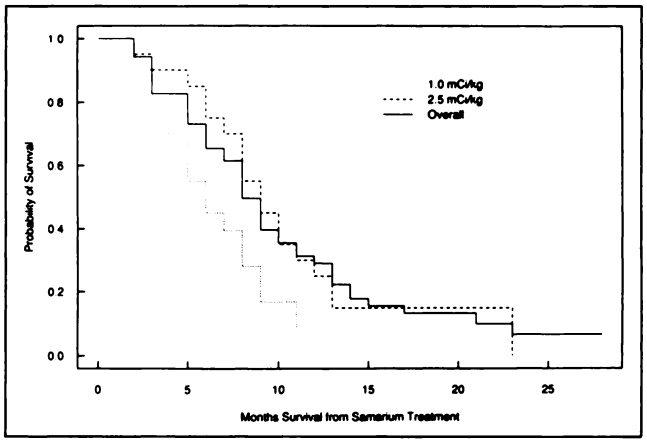

FIGURE 5. Survival after treatment with ^{153}Sm-EDTMP.

PSA and PAP levels as well as bone scans to assess disease response in our study. This group of patients had a poor prognosis based on bone scan criteria which have been shown to have prognostic significance in men with metastatic prostate cancer prior to initiation of hormonal therapy (*18*). In general, even though serial changes in PSA parallel the response of measurable disease, fluctuations in serum levels may be independent of treatment. Additionally, in hormone-refractory disease, serial changes in PSA and PAP may not correlate with measurable disease responses. In a trial of trimetrexate in hormone-refractory measurable prostate carcinoma, Scher et al. reported that there were large variations in the marker levels and that a correlation between biochemical response and measurable disease response was observed in only 47% and 68% of patients with abnormal baseline values for PAP and PSA, respectively (*18*). Subsequent analysis, however, suggested that a 50% increase from a patient's minimum value of either the PSA or PAP on two successive determinations correlated with progression in 90% of cases. A later report (*20*) suggested that patients with a >50% decline in PSA had a significantly prolonged survival than in those patients with a <50% decline. Although pain responses were evident in our study, there was no clear evidence of tumor response, either by improvement in the bone scans or significant decreases in serial PSA determinations. However, in the men treated with 2.5 mCi/kg of ^{153}Sm-EDTMP, improvement of the initial baseline value in both PSA and PAP occurred statistically more frequently than in those treated with 1.0 mCi/kg.

The goals of therapy in hormone refractory prostate carcinoma are improved quality of life and prolonged survival in this group of patients with a very poor prognosis. Median survival of men with hormone refractory prostate carcinoma is generally held to be about 6–9 mo and no intervention has ever been documented to have an impact on this survival curve. Although this was not a randomized study, there was no significant difference in prognostic factors between the patients treated with 1.0 mCi/kg and 2.5 mCi/kg of ^{153}Sm-EDTMP. Men treated with 2.5 mCi/kg of ^{153}Sm-EDTMP had a significantly longer survival compared to men treated with a 1.0 mCi/kg dosage. This study and others indicate that ^{153}Sm-EDTMP is an effective treatment for palliation of pain from bony metastases. The observed trend toward improved survival with higher treatment doses opens the possibility that this agent could be effective for treatment of bony metastatic cancer as well. Further studies are underway to examine the potential of ^{153}Sm-EDTMP in cancer treatment.

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