Samarium-153 treatment of bone pain in patients with metastatic prostate cancer

Lars J. Petersen[1], Lars Lund[2], Morten Jønler[2], Mette Jakobsen[2] & Jan Abrahamsen J[1]

ABSTRACT

INTRODUCTION: Painful bone metastases are common in advanced prostate cancer. We report the clinical outcome after administration of Samarium-153 (^{153}Sm), an emitter of beta-particles that concentrates in the areas of enhanced osteoblastic activity.

METHODS: Twenty-two patients (median age 73 years) with metastatic, hormone-refractory prostate cancer received a single bolus infusion of ^{153}Sm (37 MBq/kg). All patients had painful bone metastases to more than one anatomical region, and most had inadequate pain relief to narcotic analgesics. Bone specific pain, analgesic score according to WHO, ECOG performance status, and blood count were evaluated before and up to 28 weeks after treatment.

RESULTS: Median follow up was six weeks (mean 14 weeks). Eleven patients died within the 28 week observation period (ten from terminal disease), and four patients had their observation period truncated. Median pain score was 56.3%, 50.0%, and 50.0% of baseline values at week 4 (n = 20), 16 (n = 10), and 28 (n = 7), respectively. A reduction of baseline pain score by 50 percent or more was observed in 50%, 70% and 71% of patients at week 4, 16, and 28, respectively. Hematological toxicity was mild and reversible in most cases.

CONCLUSION: Administration of ^{153}Sm to prostate cancer patients with painful bone metastases offered clinical relevant pain relief with tolerable hematological toxicity.

Prostate cancer is one of the most common malignancies in the Western World [1]. The clinical course of metastatic bone disease is relatively long but complicated by pain and fractures which may impair quality of life. Bone pain responding inadequately to medical antitumor and analgesic therapeutics can be treated with external radiation therapy or bone-seeking isotopes. Systemic radionuclide therapy is an established alternative to external palli-ative radiotherapy for treatment of bone pain in meta-static prostate cancer [2, 3], and radionuclides are recommended by international cancer societies for palliative care of bone pain in prostate cancer [4, 5].

The most commonly used radioactive isotopes in the treatment of bone lesions in Europe are Strontium-89, (^{89}Sr) Samarium-153 (^{153}Sm), and Rhenium-186 (^{186}Re). Following systemic administration, radionuclides localizes at bone sites with increased bone turnover and irradiate tumor cells with minimal effect on normal bone [6]. Despite the substantial clinical evidence of efficacy and tolerability, radio-nuclide therapy is very infrequently used in Denmark. In this report, we present clinical data from a cohort of consecutive prostate cancer patients treated with ^{153}Sm at a single institution.

MATERIALS AND METHODS

Patients

Twenty-two consecutive patients with hormone-refractory prostate cancer (HRPC) and painful bone metastasis were treated from May 2006 through June 2008 at our hospital. Eligible HRPC patients should have painful bone metastases in more than one anatomical region, insufficient response or intolerance to opioid analgesics, and osteoblastic metastases on a bone scintigraphy. Adequate bone marrow function was required (hemoglobin > 5 mM, total white blood cell counts > 3.5 $\times$ 10^9/l, and platelet count > 100 $\times$ 10^9/l). We did not include patients with systemic chemotherapy or regional radiotherapy within six weeks, radioisotope therapy within eigth weeks, pathological fractures, or spinal cord compression.

Samarium-153 therapy

^{153}Sm-ethylenediaminetetramethylphosphonic acid (Quadramet, CIS bio international, France) (^{153}Sm) has been approved by the EMEA and FDA for relief of pain in patients with osteoblastic metastatic bone lesions at a dose of 37 MBq/kg. ^{153}Sm has an affinity for skeletal tissue and concentrates in areas of increased bone turnover. The physical half-life of the isotope is 46.3 h. Approximately 65% of the isotope is rapid deposited within the bone matrix, remainder radioactivity is removed from the circulation with residual plasma activity of 1% and < 0.1% at 4 h and 24 h, respectively. The radioisotope emits beta particles with average energy 0.81 MeV and a maximum tissue penetration of 2.5 mm (mean 0.6 mm) for localized radiotherapy [6].

ORIGINAL ARTICLE

1) Department of Clinical Physiology, and 2) Section of Urology, Department of Surgery, Viborg

Dan Med Bul 2010;57(6):A4154

TABLE 1

Demographic, clinical, and biochemical parameters of the study population

All patients, n	22
Age, years, median (range)	73 (57-84)
Duration of PC (months), median (range)	30 (3-120)
HRPC, n (%)	22 (100%)
Duration of HRPC (months), median (range)	19 (1-27)
Prior radiotherapy, n (%)	7 (32%)
Time since last therapy, months, median (range)	18 (2-34)
Prior chemotherapy, n (%)	4 (18%)
Time since last therapy, months	8 (4-10)
Prior radionuclide therapy, n (%)	5 (23%)
Time since last therapy, months	8 (5-27)
PSA, ng/ml, median (range)	197 (3-1428)
Skeletal-based pain score	14.5 (2-46)
Concurrent zoledronic acid therapy, n (%)	7 (32%)
Number of regions with pain, n (%)	
1	0
2	6 (27%)
3	7 (32%)
4	6 (27%)
5	3 (14%)
WHO medication-based pain class, n (%)	
1	0
2	3 (14%)
3	2 (9%)
4	17 (77%)
ECOG performance status, n (%)	
0	0
1	15 (68%)
2	1 (5%)
3	4 (18%)
4	2 (9%)

ECOG = Eastern Cooperative Oncology Group; HRPC = hormone-refractory prostate cancer; PC = prostate cancer; WHO = World Health Organization.

^{153}Sm was administered as a weight-adjusted dose of 37 MBq/kg as an intravenous infusion over 3 min. Patients was admitted in an isolation bed room for 24 h or until the radiation was below 20 mSv/h measured with a handheld dose rate monitor.

Efficacy and safety assessments

Medical data were captured from patient records and telephone questionnaires performed at week 4, 16, and 28 after therapy. Local procedure guidelines recommended hematological safety monitoring every two weeks for six weeks after therapy or until recovery from hematological toxicities. The maximum decrease in hematological parameters during the first 16 weeks after ^{153}Sm was used for classification of hematological toxicity using Common Toxicity Criteria Adverse Event 3.0 criteria. Performance status was evaluated using Eastern Cooperative Oncology Group (ECOG) criteria. No ethical approval or informed consent was required or obtained for this type of quality control trial with the use of questionnaires as the only tool used in addition to normal clinical controls.

Pain intensity was graded by the patients as absent, mild, moderate, severe, or unbearable (0-4 points), and pain frequency was assessed as none, occasional, intermittent, frequent, or constant (0-4 points) [7]. The sum of pain intensity and pain frequency was scored for five anatomical segments and summed to a maximum pain score of 80. The five-point WHO pain score was calculated based on medical records (level 0, analgesics not required; level 1, non-narcotic analgesics required occasionally; level 2, non-narcotic analgesics required regularly; level 3, narcotic analgesics required occasionally; and level 4, narcotic analgesics required regularly).

RESULTS

Patient characteristics are shown in **Table 1**. All HRPC patients had widespread skeletal involvement with painful metastases in at least two anatomical. Most patients were resistant to opioid analgesics. A large proportion of patients have received prior palliative radiotherapy and/or systemic chemotherapy. About one third of the patients received zoledronic acid for prevention of skeletal-related events, and they continued this treatment during ^{153}Sm therapy.

Median time for follow up was six weeks (mean 14 weeks). Seven patients (32%) were followed for 28 weeks. Four patients (18%) had their observation period truncated due to initiation of additional palliative intervention (two patients received radiotherapy at week 4 and 16, and two patients received chemotherapy at week 6 and 16, respectively). Finally, 11 patients (50%) died within the 28-week observation period: Ten patients died from terminal cancer, and one patient suffered from a fatal cerebral hemorrhage. No fatalities were associated with treatment-induced toxicity.

Pain assessment

Median bone specific pain score was 14.5 (range 2-46, n = 22) at baseline (**Figure 1**). A total of 20 of 22 patients had at least one pain score after baseline, including 15 (75%) patients with reduced pain at any visits during follow-up, three (15%) non-responders, and two (10%) patients with progressing pain versus baseline. The median pain values were 5 (1-18, n = 20), 3.5 (0-18, n = 10), and 1 (0-34; n = 7) at week 4, 16, and 28, respectively, corresponding to median values of 56.3%, 50.0% and 50.0% of baseline pain at week 4, 16, and 28. Pain responses in four patients with prior radionuclide treatments were 71.1%, 60.3%, and 50% of baseline at week 4, 16, and 28, respectively. Reduction of baseline pain score by 50 percent or more was observed in 50%,

70% and 71% of patients at week, 4, 16, and 28, respectively. Median WHO pain class, based on actual drug administration, remained unchanged during the observation period (median level 4 at all visits).

Safety assessment

Most patients had grade 1-2 anemia at baseline (**Table 2**). The hematological toxicities following ^{153}Sm treatment were modest (grade 1-2) in most cases with nadir at week 4 for platelets and week 2-6 for white blood cells. Two patients showed reversible grade 3 thrombocytopenia with nadir at week 4. One patient, presenting with grade 1 thrombocytopenia and anemia as baseline, developed a slowly progressing loss of bone marrow function with grade 4 thrombocytopenia and grade 3 anemia but no leucopenia at week 6. His clinical condition was rapidly deteriorating, and he died eight weeks after ^{153}Sm therapy despite relevant replacement therapy with platelets and erythrocyte suspensions. His PSA levels rose from 912 ng/ml at baseline to values above 3,000 ng/ml at week 2. He had received prior radiotherapy and chemotherapy and two prior treatments of ^{153}Sm without hematological complications. The responsible physician classified the event as being unrelated to ^{153}Sm therapy.

DISCUSSION

Bone pain constitutes a major clinical challenge in metastatic HRPC, in particular when the pain becomes resistant to opioid analgesics. Local palliative radiotherapy is suitable for localized lesions, but less applicable in patients with widespread bone lesions. The aim is to give these patients a better quality of life with the minimum use of drugs which could comprise their daily activity. Our results confirm that radionuclide therapy with ^{153}Sm is a feasible treatment opportunity in patients with HRPC and wide-spread, painful bone metastases. We cannot exclude some selection bias on the pain outcome, since a proportion of patients were not followed for 28 weeks but died from their disease. However, a notable reduction in pain was observed at week 4 where a large proportion of the patients were still available for follow-up. The proportion of patients obtaining a 50% reduction or more of baseline pain was 70 percent or more at week 16-28. The overall results are in line with data presented in randomized controlled trials and in large observational studies [2, 3, 7]. There appears to be no clear difference in clinical efficacy among available radionuclides, which induce clinical relevant pain relief and complete pain relief in 50-95% and 20-30% of patients, respectively. The numbers need to be treated to obtain complete pain relief is 4 [2].

The observed survival of the patients was short. Median survival was only six weeks (mean 14 weeks) despite an expected survival of 12 weeks was required in order to receive ^{153}Sm therapy. For this reason, it was not possible to analyze duration of pain relief. In trials with patients with less advanced disease, duration of pain relief is usually in a range of 1-6 months [2]. Relief of bone pain was not associated with change in ECOG performance score. However, the patients in general showed rapidly deteriorating disease with doubling of mean PSA during the observation period. It seems difficult to demonstrate improvement in performance score in such a population. In other studies with less advanced disease, pain relief of ^{153}Sm therapy has been shown to improve performance evaluated by Karnofsky performance score [8]. Radionuclides are not restricted for relief

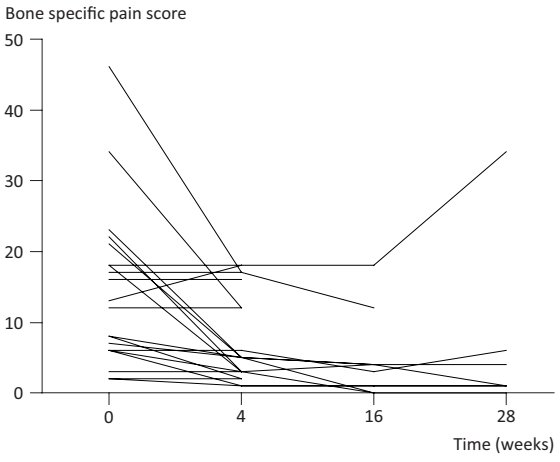
TABLE 2

Hematological toxicity classified in accordance with Common Toxicity Criteria Adverse Event 3.0 criteria.

	Grade			
	1	2	3	4
Hemoglobin				
Baseline, n	14	1	0	0
During 16 week follow-up, n	13	6	1	0
White blood cells				
Baseline, n	0	0	0	0
During 16 week follow-up, n	1	3	0	0
Platelets				
Baseline, n	2	0	0	0
During 16 week follow-up, n	6	1	2	1

FIGURE 1

Individual bone-specific pain score in 22 patients with metastatic prostate cancer before and after treatment with ^{153}Sm. Median score was 14.5 at baseline (week 0), and declined to 5 (n = 20), 3.5 (n = 10), and 1 (n = 7) at week 4, 16, and 28, respectively. Loss of follow-up was mainly due to cancer-related deaths and truncated data due to prohibited concurrent medication. Please refer to the Results section for further details.



of opioid resistant pain only. Several trials have shown a very favorable long-term efficacy and tolerability profile in patient with no need of opioid or in patients being pain-free on such drugs [8]. Despite zoledronic acid may influence bone metabolism, bone uptake of ^{153}Sm or clinical efficacy of radionuclides has been shown not to be affected by concomitant therapy with bisphosphonates [9].

The hematological toxicity was mild, acceptable and fully reversible without the use of replacement therapies or stem cell growth factor support. The hematological toxicity showed nadir at week 4-6 as previously reported [9, 10]. Two episodes of reversible grade 3 thrombocytopenia were observed within the expected time window of radionuclide toxicity. One late fatal case of bone marrow dysfunction was classified as disease progression rather than myelotoxicity from ^{153}Sm therapy. The time course of bone marrow impairment, excellent tolerability to two previous ^{153}Sm therapies, and lack of effect of replacement therapies supported this conclusion. ^{153}Sm has a wide therapeutic window and dose-finding studies have shown that doses up to 111 MBq/kg is safe but associated with increased number of episodes of reversible hematological events [11]. In addition, the cumulated toxicity is low. Repeated dosing for up to 4-5 treatments with radionuclides has been shown to be safe and effective [12].

Randomized, controlled trials have shown radioisotopes to induce pain relief not significant different from external palliative radiotherapy [13, 14]. The impact on radionuclides on survival is controversial. A significantly reduced survival was reported with ^{89}Sr versus local field radiotherapy for bone pain in metastatic prostate cancer in a European randomized, multi-center trial [13]. These data are in direct contrast to data from a very similar trial from the UK where no difference in survival was observed among patients who received ^{89}Sr and palliative radiotherapy [14]. Improved survival have been reported with radioisotopes in randomized, placebo-controlled trials [15].

Patient with HRPC should initially be considered for palliative chemotherapy with documented effect on survival and pain relief [16]. Radionuclide therapy has obtained regulatory approval for pain relief only. Recent or concurrent systemic chemotherapy has so far been regarded contraindications for radionuclide administration. However, the combined use of radionuclides and chemotherapy may act synergistically and improve pain palliation [17]. Several reports have reported improvement in pain relief, prolonged duration of responses, reduced development of new painful sites, improved progression-free survival and overall survival of radioisotopes with chemotherapy versus chemotherapy alone in prostate cancer [17, 18]. The combination of radioisotopes and chemotherapy, including docetaxel, is currently pursued in several clinical trials.

It is estimated that approximately 1,100 men die annually in Denmark from metastatic prostate cancer [19]. Based on efficacy, tolerability, ease of administration, and minimal latency from referral to treatment, it is noteworthy that only 14-16 patients received radionuclides annually in Denmark 2007-2008 (Klaus Ennow, National Institute of Radiation Hygiene, personal communication). In comparison, 21% and 40% of US oncologist used radionuclides alone or in combination with local field radiotherapy, respectively, in patients with prostate cancer [20]. We conclude that radionuclide therapy should be considered an option among palliative modalities in HRPC patients with multiple painful bone metastases.

CORRESPONDENCE: *Lars J. Petersen,* Department of Clinical Physiology, Viborg Hospital, 8800 Viborg, Denmark. E-mail: lars.j.petersen@viborg.rm.dk

ACCEPTED: 15 March 2010

CONFLICTS OF INTEREST: None

ACKNOWLEDGEMENTS: Nurse *Begitte H. Pedersen* is thanked for skillful support.

LITERATURE

1. Damber JE, Aus G. Prostate cancer. Lancet 2008;371:1710-1721.
2. Roque M, Martinez MJ, Alonso P et al. Radioisotopes for metastatic bone pain. Cochrane Database Syst Rev 2003;CD003347.
3. Bauman G, Charette M, Reid R et al. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radiother Oncol 2005;75:258-270.
4. Scherr D, Swindle PW, Scardino PT. National Comprehensive Cancer Network guidelines for the management of prostate cancer. Urology 2003;61:14-24.
5. Horwich A, Parker C, Kataja V. Prostate cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:76-78.
6. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. Semin Nucl Med 2010;40:89-104.
7. Dafermou A, Colamussi P, Giganti M et al. A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. Eur J Nucl Med 2001;28:788-798.
8. Liepe K, Kropp J, Runge R et al. Therapeutic efficiency of rhenium-188-HEDP in human prostate cancer skeletal metastases. Br J Cancer 2003;89:625-629.
9. Lam MG, de Klerk JM, van Rijk PP et al. Bone seeking radiopharmaceuticals for palliation of pain in cancer patients with osseous metastases. Anticancer Agents Med Chem 2007;7:381-397.
10. Sartor O, Reid RH, Bushnell DL et al. Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain. Cancer 2007;109:637-643.
11. Collins C, Eary JF, Donaldson G et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. J Nucl Med 1993;34:1839-1844.
12. Kasalicky J, Krajska V. The effect of repeated strontium-89 chloride therapy on bone pain palliation in patients with skeletal cancer metastases. Eur J Nucl Med 1998;25:1362-1367.
13. Oosterhof GO, Roberts JT, de Reijke TM et al. Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. Eur Urol 2003;44:519-526.
14. Quilty PM, Kirk D, Bolger JJ et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. Radiother Oncol 1994;31:33-40.
15. Buchali K, Correns HJ, Schuerer M et al. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. Eur J Nucl Med 1988;14:349-351.
16. Petrioli R, Fiaschi AI, Francini E et al. The role of doxorubicin and epirubicin in the treatment of patients with metastatic hormone-refractory prostate cancer. Cancer Treat Rev 2008;34:710-718.
17. Sciuto R, Festa A, Rea S et al. Effects of low-dose cisplatin on 89Sr therapy for painful bone metastases from prostate cancer: a randomized clinical trial. J Nucl Med 2002;43:79-86.
18. Tu SM, Millikan RE, Mengistu B et al. Bone-targeted therapy for advanced

androgen-independent carcinoma of the prostate: a randomised phase II trial. Lancet 2001;357:336-341.
19. Kvale R, Auvinen A, Adami HO et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. J Natl Cancer Inst 2007;99:1881-1887.
20. Ben-Josef E, Shamsa F, Williams AO et al. Radiotherapeutic management of osseous metastases: a survey of current patterns of care. Int J Radiat Oncol Biol Phys 1998;40:915-921.