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Palliative effects and adverse events of strontium-89 for prostate cancer patients with bone metastasis

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Abstract. The aim of the present study was to evaluate the palliative effects and adverse events of strontium-89 (Sr-89) in patients with bone metastasis from prostate cancer. A total of 18 patients with prostate cancer and painful bone metastases, as diagnosed on bone scintigraphy, who were treated with Sr-89 at the National Kyushu Cancer Center between February, 2008 and April, 2014 were reviewed. Of the 18 subjects, 13 (72.2%) achieved a pain response, whereas 5 were classified as pain non-responders (27.8%). According to a logistic regression analysis, the pre-administration characteristics, including age, prostate-specific antigen (PSA), alkaline phosphatase (ALP), history of bone-modifying agent administration, opioid use or palliative radiation therapy, time after the combined androgen blockade nadir and time since the pain onset, were not found to be significant predictors of the pain response. Similarly, the post-administration characteristics, including pain flares and the PSA and ALP response, were not found to be significant predictors of the pain response. Although no patients exhibited leukocyte toxicities, 2 patients experienced myelosuppression, involving anemia and thrombocytopenia, requiring transfusion of red cell or platelet concentrate following Sr-89 treatment. Of the 18 patients, 5 (27.8%) reported pain flares, all of whom were successfully treated with rescue drugs alone. According to the logistic regression analysis, of the pre-administration characteristics, only ALP was identified as a significant predictor of bone marrow suppression in the univariate and multivariate analyses (P=0.006). Therefore, Sr-89 treatment was found to be effective in ameliorating bone pain associated with metastasis from prostate cancer. Although it is difficult to identify the patients who will receive pain relief prior to Sr-89 administration, this drug should be administered during the early stages due to the potential for bone marrow suppression in patients with high ALP levels.

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Introduction

The bone is the most common site of metastasis in prostate cancer patients, with bone metastases occurring in ~65-75% terminal cases of prostate cancer. Androgen deprivation therapy (ADT) is commonly used for advanced-stage disease, such as that involving multiple bone metastases, with significant effects on the primary tumor as well as the bone metastases. Symptoms, such as pain, improve in almost all patients, with a median survival period of 36 months and a 5-year survival rate of 25% (1-3). However, decreases in the effectiveness of ADT are increasingly being reported, with cancer ultimately progressing to castration-resistant prostatic cancer (CRPC) and pain control is a compelling issue in CRPC patients with bone metastasis. Unlike drug treatment with analgesics, radiation therapy is extremely effective in achieving pain relief in bone metastasis patients. However, the use of hemibody irradiation to treat widespread bone metastases may induce severe bone marrow toxicity (4,5). Strontium-89 (Sr-89) is a pure β-emitter with a half-life of 50.5 days. Blake *et al* (6) demonstrated that Sr-89 follows the biochemical pathway of calcium within the bone, is preferentially taken up at sites of increased bone turnover, irrespective of the primary tumor where it remains over a more prolonged period of time compared to the normal bone tissue from which it is rapidly washed; therefore, maximal activity is observed at sites of bone metastases following the administration of this drug. The range of β particles in bone tissues is short (3 mm); hence, Sr-89 is associated with a relatively low rate of hematological toxicities (6).

Outside Japan, Sr-89 has been used since the 1990's and its efficacy has been demonstrated. However, this drug was only introduced in Japan in July, 2007 and thus far there have been few reports on the administration of strontium in Japanese prostate cancer patients. Therefore, in order to elucidate the effectiveness and adverse events of Sr-89 for the treatment of bone metastasis from prostate cancer in Japanese patients, we retrospectively reviewed cases treated at our institution.

Materials and methods

Patients. A total of 18 prostate cancer patients with painful bone metastases, as diagnosed on bone scintigraphy, who were treated with Sr-89 at the National Kyushu Cancer Center, Fukuoka, Japan, between February, 2008 and April, 2014, were retrospectively reviewed. Written informed consent was

obtained from all the patients prior to the initiation of treatment and the study protocol was approved by the Institutional Ethics Committee. The inclusion criteria were persistent pain despite the use of analgesics and a life expectancy of >3 months. The main exclusion criteria were disseminated intravascular coagulation, a significantly degraded renal function or severe bone marrow suppression (white blood cell count <2,000/mm^3, platelet count <50,000/mm^3 and hemoglobin level <8 g/dl). Pain response assessments and blood tests were conducted prior to and biweekly after Sr-89 injection for 3 months. Sr-89 was administered via intravenous injection at a dose of 2 MBq/kg to a maximum of 141 MBq per patient. If the patient received ≥2 courses of Sr-89, only the first injection of Sr-89 was included in the analysis.

Pain assessment. Information regarding pain and analgesic effect was obtained via a physician interview using the visual analog scale (VAS). Patients who exhibited a reduction in the VAS score from baseline were defined as pain responders, while the remaining subjects were classified as pain non-responders.

Prostate-specific antigen (PSA) and serum alkaline phosphatase (ALP) response and toxicity. Patients who exhibited a reduction in the PSA level from baseline, even if only marginal, were defined as PSA responders, whereas the remaining subjects were defined as PSA non-responders. Similarly, patients who exhibited a reduction in the serum ALP level from baseline, were defined as ALP responders, while the remaining subjects were classified as ALP non-responders. The toxicities were graded using the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis. The statistical analyses were conducted using the JMP® Pro software package, version 9.0.2 (SAS Institute, Inc., Cary, NC, USA). The Mann-Whitney U test and χ^2 test were used to assess differences between pain responders and non-responders and between patients with and those without myelosuppression. The significance of the clinical parameters associated with improvements in bone pain and myelosuppression following Sr-89 treatment was assessed using a logistic regression analysis. A P-value of <0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The baseline characteristics of the 18 patients who underwent Sr-89 therapy are summarized in Table I. With respect to analgesic treatment, opioids were used in 11 patients (61.1%). Regarding prior treatment for prostate cancer, all the patients had a history of combined androgen blockade (CAB) therapy and 8 patients (44.4%) had a history of bone-modifying agent (BMA) administration. The anticancer agent docetaxel was used in 4 cases (22.2%) and estramustine phosphate was administered to 3 patients (16.7%). A total of 6 patients (33.3%) received palliative external-beam radiotherapy (EBRT) to symptomatic sites of bone metastasis prior to Sr-89 treatment.

Patient characteristics according to the pain response. The results regarding pain response are shown in Table II. A total of 13 patients (72.2%) achieved a pain response, whereas 5 patients (27.8%) were classified as pain non-responders. The correlations between the patient characteristics and pain response are presented in Table III. According to the logistic regression analysis, the pre-administration characteristics, including age, PSA, ALP, history of BMA, opioid use and palliative radiation therapy, duration from CAB nadir and the time since pain onset, were not found to be significant predictors of the pain response. Similarly, the post-administration characteristics, including pain flares and the PSA and ALP response, were not significant predictors of the pain response.

Table I. Baseline patient characteristics.

Characteristics	Patient no. (%) (n=18)
Age, years	
Median (range)	76 (60-86)
PSA, ng/ml	
Median (range)	50.628 (1.764-2,017.400)
ALP, IU/l	
Median (range)	973 (248-2,944)
Site of metastasis	
Bone	11 (61.1)
Bone+lymph node	7 (38.9)
Analgesics	
NSAIDs	11 (61.1)
Opioid + NSAIDs	7 (38.9)
Prior treatment	
Combined androgen blockade	18 (100.0)
Radiation therapy	9 (50.0)
Bone-modifying agents	8 (44.4)
Steroids	7 (38.9)
Docetaxel	4 (22.2)
Radical prostatectomy	3 (16.7)
Estramustine phosphate	3 (16.7)
Ethinylestradiol	3 (16.7)
Palliative radiation therapy	6 (33.3)

PSA, prostate-specific antigen; ALP, alkaline phosphatase; NSAIDs, non-steroidal anti-inflammatory drugs.

Toxicities. The toxicities occurring within 3 months following Sr-89 therapy are listed in Table IV. While no patients exhibited leukocyte toxicities in this study, 2 patients experienced myelosuppression, involving anemia and thrombocytopenia, requiring the transfusion of red cell or platelet concentrate following administration of Sr-89. Of the 18 patients, 5 (27.8%) reported pain flares, all of whom were successfully treated with rescue drugs alone.

Patient characteristics according to bone marrow suppression. The results regarding bone marrow suppression are shown in Table V. A total of 16 patients (88.9%) did not exhibit bone marrow suppression, whereas only 2 patients experi-

Table II. Patient characteristics according to the pain response.

Characteristics	Response (n=13)	No response (n=5)	P-value
Age, years			0.522
Median (range)	76 (60-86)	73 (63-79)	
PSA, ng/ml			0.888
Median (range)	25.448 (1.822-1,130.300)	795.710 (1.764-2,017.400)	
ALP, IU/l			0.255
Median (range)	912 (248-2,204)	1,034 (373-2,944)	
History of opioid use			0.952
Yes	5	2	
No	8	3	
History of palliative radiation therapy			0.710
Yes	4	2	
No	9	3	
History of BMA			0.410
Yes	5	3	
No	8	2	
Time since pain onset, days			0.402
Median (range)	489 (21-2,359)	168 (26-1,349)	
Time since CAB nadir, days			0.805
Median (range)	684 (92-2,340)	658 (-163-2,147)	
Pain flare			0.648
Yes	4	1	
No	9	4	
PSA response			0.183
Increase	10	4	
Decrease	3	1	
ALP response			0.730
Increase	4	3	
Decrease	9	2	

PSA, prostate-specific antigen; ALP, alkaline phosphatase; BMA, bone-modifying agent; CAB, combined androgen blockade.

Table III. Univariate analysis of the correlations between patient characteristics and pain response.

Characteristics	Odds ratio	P-value	95% CI
Age	0.958	0.539	0.834-1.100
PSA	1.002	0.191	1.000-1.004
ALP	1.001	0.386	0.999-1.002
History of opioid use	1.067	0.952	0.129-8.795
History of palliative radiation therapy	1.500	0.711	0.176-12.778
History of BMA	2.400	0.416	0.291-19.7899
Time since pain onset	0.999	0.538	0.998-1.001
Duration from CAB nadir	1.000	0.735	0.998-1.001
Pain flare	0.563	0.650	0.047-6.771
PSA response	1.200	0.888	0.094-15.264
ALP response	3.375	0.266	0.396-28.751

PSA, prostate-specific antigen; ALP, alkaline phosphatase; BMA, bone-modifying agent; CAB, combined androgen blockade; CI, confidence interval.

Table IV. Toxicity within 3 months after strontium-89 administration.

	Grade, no. (n=18)		
Toxicities[a]	3	4	3 or 4 (%)
Leukopenia	0	0	0 (0.0)
Anemia	0	2	2 (11.1)
Thrombocytopenia	1	0	1 (5.6)
Pain flare			5 (27.8)

[a]Defined according to the Common Terminology Criteria for Adverse Events.

Table V. Patient characteristics according to the degree of bone marrow suppression.

Characteristics	Myelosuppression (n=2)	No myelosuppression (n=16)	P-value
Age, years			0.206
Median (range)	68 (63-73)	76 (60-86)	
PSA, ng/ml			0.092
Median (range)	822.360 (795.710-849.010)	33.702 (1.764-2,017.400)	
ALP, IU/l			0.035
Median (range)	2,403 (1,861-2,944)	896 (248-2,204)	
History of opioid use			0.732
Yes	1	6	
No	1	10	
History of palliative radiation therapy			0.595
Yes	1	5	
No	1	11	
History of BMA			0.867
Yes	1	7	
No	1	9	
Time since pain onset, days			0.482
Median (range)	342 (26-658)	459 (21-2,359)	
Time since CAB nadir, days			0.673
Median (range)	566 (474-658)	796 (-163-2,340)	

PSA, prostate-specific antigen; ALP, alkaline phosphatase; BMA, bone-modifying agent; CAB, combined androgen blockade.

Table VI. Analysis of the correlations between the patient characteristics and bone marrow suppression.

	Univariate analysis			Multivariate analysis		
Characteristics	Odds ratio	P-value	95% CI	Odds ratio	P-value	95% CI
Age	0.898	0.290	0.695-1.096			
PSA	1.001	0.234	0.999-1.004			
ALP	1.004	0.006	1.000-1.012	1.004	0.006	1.000-1.012
History of opioid use	1.667	0.735	0.058-47.734			
History of palliative radiation therapy	2.200	0.605	0.076-63.848			
History of BMA	1.286	0.867	0.045-36.557			
Time since pain onset	0.999	0.469	0.993-1.001			
Time since CAB nadir	0.999	0.450	0.996-1.001			

PSA, prostate-specific antigen; ALP, alkaline phosphatase; BMA, bone-modifying agent; CAB, combined androgen blockade; CI, confidence interval.

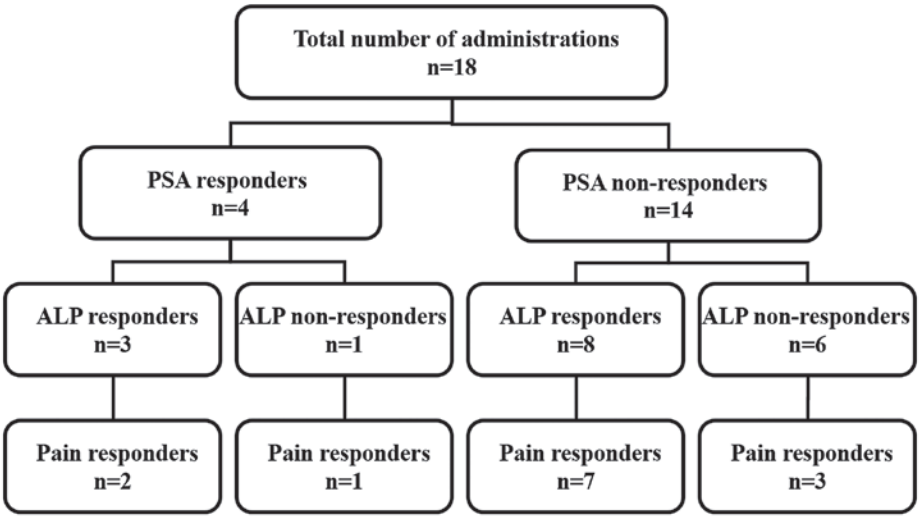

Figure 1. Associations between the changes in the prostate-specific antigen (PSA) and alkaline phosphatase (ALP) values and the pain response.

enced bone marrow suppression. The correlations between the patient characteristics and bone marrow suppression are presented in Table VI. According to the logistic regression analysis, of the pre-administration characteristics, only ALP was a significant predictor of bone marrow suppression in the univariate and the multivariate analyses (P=0.006).

Association between changes in the PSA and ALP values and the pain response. Among the 18 patients, the PSA level decreased in 4 subjects, among whom the ALP level decreased in 3 patients, 2 of whom reported improvements in bone pain. The PSA level increased in 14 patients, among whom the ALP level decreased in 8 patients, 7 of whom experienced pain improvement (Fig. 1).

Discussion

The use of Sr-89 chloride therapy to treat painful bone metastases was first reported in 1942 by Pecher (7). Since then, several phase III studies (8-11) have demonstrated the usefulness and cost-effectiveness of Sr-89 as either an alternative or adjunct to EBRT in males with bone pain resulting from metastatic prostate cancer. In Japan, a phase III clinical trial of Sr-89 was conducted in 1995; however, approval for this drug was not obtained, due to problems with the evaluation method (12). Although Sr-89 subsequently obtained manufacturing approval in July, 2007, thus far there have been only few reports describing its administration to Japanese prostate cancer patients, compared to the findings reported in Europe and the United States of America. Therefore, in order to elucidate the effectiveness and adverse events of Sr-89 for the treatment of bone metastasis from prostate cancer in Japanese patients, we retrospectively reviewed relevant cases treated at our institution.

As regards the palliative efficacy of Sr-89, 13 patients (72.2%) in this study achieved a pain response (Table II), based on decreases in their VAS score. The majority of the previous studies have used scoring systems; however, differences in the criteria have complicated the analyses of data, although the definitions of a complete response and lack of response are straightforward. The proportion of patients classified as complete responders to Sr-89 ranges between 8 and 77% (mean, 32%), while that of patients exhibiting no response ranges between 14 and 52% (mean, 25%). Within this range, 44% of patients display some degree of response to Sr-89 treatment, resulting in a mean overall response rate of 76% (13). Therefore, the administration of Sr-89 for the treatment of prostate cancer in Japanese patients is expected to exert an analgesic effect and achieve some pain relief.

We then investigated the characteristics of patients who experienced pain relief following Sr-89 administration. Consequently, the patients administered Sr-89 in this study were divided into two groups, namely the pain response group and the non-response group (Table II). No significant differences were observed between the two groups. The correlations between the patient characteristics and the pain response were subsequently analyzed using a logistic regression analysis. However, there were no significant differences in the pre-administration factors, including age, PSA, ALP, history of opioid use, palliative radiation and BMA, time since the CAB nadir and time since pain onset, according to the univariate and multivariate analyses (Table III). Based on these results, Sr-89 was shown to be effective in pain management for prostate cancer patients with bone metastasis, although it is difficult to identify patients who will benefit from this drug prior to treatment. In a study by Kraeber-Bodéré F *et al* (14), the patients were classified into two groups according to the number of foci suggestive of metastases on bone scintigraphy, namely the ≤10 (moderate bone involvement) and >10 (extensive bone involvement) foci groups. In that study, the overall response rate (77 and 75%, respectively) was not significantly different between the two groups, whereas the rate of complete response was significantly higher in the group with ≤10 foci (54 vs. 24%; P=0.005) (14). Sr-89 is effective in patients with early-stage bone metastasis, while the pain relief effect is lower and adverse events are more severe in patients with end-stage bone metastasis (15-17). Therefore, Sr-89 therapy is considered to exert a positive effect against pain, even when the bone metastasis is not extensive. However, a pain relief effect may also be obtained in patients with extensive bone

metastasis, although it is difficult to precisely predict the effect prior to Sr-89 administration (18). These reports support the present findings.

We then examined the adverse events associated with the administration of Sr-89 (Table IV). Finlay *et al* (13) reported that the toxic effects associated with Sr-89 are mild and reversible. Approximately 15% of the patients experience increased pain or flares after 1-5 days, which may last for 4 days. A previous trial reported that pain flares were associated with a good response to Sr-89 (19); by contrast, a multicenter trial reported that such flares are not associated with the effect of Sr-89 treatment (20). Therefore, the clinical significance of pain flares remains unclear. In this study, 5 of the 18 patients (27.8%) reported pain flares (Table IV); however, pain flares were not found to be a significant predictive factor of the pain response (P=0.650, Table III). Finlay *et al* (13) reported toxic hematological effects to be the most commonly observed side effects, with a reduction in the white blood cell count of 11-65% in 12-80% of the patients. In addition, the platelet count has been reported to decrease by an average of 29% in 29-80% of the patients, whereas changes in the red cell count are negligible or non-existent. Generally, these blood parameters return to normal without intervention. Moreover, previous trials have found no significant changes in the hematological variables associated with Sr-89 use (13). In this study, grade 4 anemia was observed in 2 patients (11.1%) and grade 3 thrombocytopenia in 1 patient (5.6%), as shown in Table IV. These cases overlapped and all the patients required blood transfusions. The patients who were administered Sr-89 were divided into two groups, namely the myelosuppression and no myelosuppression groups (Table V), with significant differences in the PSA and ALP values between the two groups (P=0.092 and 0.035, respectively). The correlations between the patient characteristics and myelosuppression were subsequently analyzed using a logistic regression analysis, which identified ALP level as the only significant factor affecting the incidence of bone marrow suppression in the univariate and multivariate analyses (P=0.006, Table VI). Based on these results, physicians should pay more attention when administering Sr-89 to patients with high ALP values, which suggest extensive bone metastasis, due to the potential for bone marrow suppression. Furthermore, Sr-89 should be administered before bone metastases become widespread, as less favorable responses and higher toxicity have been reported in patients with end-stage disease. For example, a study by Rogers *et al* (21) on 60 patients with widespread symptomatic disease treated with Sr-89 at a dose of 66.6-173.9 MBq (median, 133.2 MBq) (1.8-4.7 mCi [median, 3.6 mCi]) reported an overall response rate of 67% at 7-11 weeks. In that study, 3 patients (6%) exhibited severe thrombocytopenia and bleeding diathesis at the time of death at 10, 12 and 16 weeks after injection. Lee *et al* (22) further reported unfavorable results in 28 patients with end-stage disease treated with Sr-89 at a dose of 81.4-162.8 MBq (2.2-4.4 mCi). In that report, only 29% of the patients experienced moderate to significant pain relief, 32% exhibited some relief and 50% reported no pain relief. That group of patients exhibited a median survival of only 23 weeks and 32% of the subjects required additional palliative EBRT. In addition, the patients displayed a significant reduction in their blood counts. Among patients with end-stage bone metastasis, due to bone marrow suppression following prior treatment with external irradiation and chemotherapy and the infiltration of the bone marrow by the tumor, the standby capacity of the bone marrow may already significantly decreased prior to Sr-89 administration. Therefore, bone marrow suppression may be synergistically enhanced in patients with extensive bone metastasis compared to those with fewer bone metastatic lesions, as the degree of bone marrow suppression is associated with the proportion of Sr-89 accumulated and retained in the bone, which is relatively increased in such patients.

Finally, we investigated the association between changes in the PSA and ALP levels according to the extent of pain improvement associated with bone metastasis. As shown in Fig. 1, a PSA response was observed in 4 cases (22.2%) and an ALP response was observed in 11 cases (61.1%); however, there were no fixed trends in the changes in the PSA or ALP values according to the pain response. Similar results were obtained in the logistic regression analysis, as shown in Table III (PSA responders, P=0.888; ALP responders, P=0.266). Therefore, changes in the characteristics of the patients are not necessarily associated with the pain improvement effect. Previous trials on hormone-refractory prostate cancer patients have reported changes in tumor markers following treatment with Sr-89. For example, a decrease of >50% was observed in the serum PSA level in 37% of the patients in a previous study (20). However, another study demonstrated a mean increase of 36% in the PSA concentration from the pretreatment period to 2 months after treatment, whereas the ALP concentration decreased by 20% (23). Those reports also support the findings of our study. When Sr-89 was first released in Japan, it was recommended in the manual that it should be administered only to patients with bone pain that could not be controlled with other common pain relief methods. However, the manual was revised in February, 2013 and now specifies that Sr-89 may be used at any stage in the analgesic ladder, based on the criteria of the World Health Organization (WHO). In accordance with this revision, Sr-89 may be administered in the early stage of bone metastasis and applied clinically more effectively and safely.

Sr-89 is very effective in ameliorating bone pain in Japanese prostate cancer patients. Although it is difficult to predict which patients will achieve pain relief from Sr-89 prior to administration, this drug should be administered during the early stages of bone metastasis, due to the potential for bone marrow suppression in patients with high ALP levels.

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