Concurrent use of Sr-89 chloride with zoledronic acid is safe and effective for breast cancer patients with painful bone metastases

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Abstract. Our aim in this study was to examine the safety and efficacy of the concurrent use of the radiopharmaceutical strontium-89 (Sr-89) chloride with zoledronic acid in standard anticancer therapy for breast cancer patients with painful multifocal bone metastases. The study comprised 16 breast cancer patients with painful multifocal bone metastases detected by bone scintigraphy, computed tomography or magnetic resonance imaging. All patients were treated with Sr-89 and zoledronic acid concurrently between March 2007 and February 2011 as part of a standard therapeutic regimen comprising chemotherapy, endocrine therapy, molecular targeting therapy and targeted radiotherapy. Sr-89 was administered intravenously at 2 MBq/kg to a maximum of 141 MBq per person. Safety was evaluated according to myelotoxicity as measured by the Common Terminology Criteria for Adverse Events (v3.0). To assess treatment efficacy, we monitored changes in analgesic drug dosages. Furthermore, bremsstrahlung imaging after the administration of Sr-89 was utilized to examine the relationship between the accumulation of Sr-89 in metastatic sites and treatment efficacy. Based on the results, a total of 14 out of 16 patients (88%) reported bone pain relief, indicating a high efficacy of Sr-89 combined with zoledronic acid. In responsive cases, a strong uptake of Sr-89 was observed on bremsstrahlung imaging at the same sites indicated by ^{99m}Tc bone scintigraphy. Moreover, severe myelosuppression (> grade 3) was not observed, and adverse events were tolerable. In conclusion, the use of Sr-89 with zoledronic acid in breast cancer patients with painful bone metastases was safe and effective when administered concurrently with other standard therapies. In the future, the treatment with Sr-89 at the early stage should be considered, and a large-scale clinical study should be conducted.

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Introduction

Bone metastasis occurs in approximately 80% of patients with advanced breast cancer. Twenty to eighty-five percent of all cancer patients show bone metastasis during the clinical course, regardless of cancer type. Sixty-five to seventy-five percent of these suffer from intolerable pain (1-3). Since the goal of treatment in advanced cancer patients is to prolong survival and improve their quality of life (QOL), pain relief is crucial. In clinical practice, the World Health Organization (WHO) 3-Step Pain Removal Ladder System, in which non-steroidal anti-inflammatory drugs (NSAIDs), weak opioids and strong opioids are administered for pain relief using a multistep system, is commonly employed.

Clinical studies of bisphosphonates have been conducted in breast and prostate cancer patients, in whom the incidence of bone metastasis is reportedly high. These studies demonstrated that bisphosphonates decreased the incidence of skeletal-related events associated with radiotherapy or surgery for bone metastasis-related fracture or bone pain. In addition, these agents relieve bone pain, maintaining the QOL of patients with bone metastasis, and therefore they are standard agents for the management of bone metastasis in clinical practice.

In 2006, zoledronic acid was approved in Japan for the treatment of bone metastasis from other solid cancers, in addition to that from breast cancer and multiple myeloma. A pre-clinical study showed that bisphosphonates exhibited a variety of antitumor effects, such as the prevention of bone metastasis, induction of cancer cell apoptosis, antineovascularization actions and induction of γ/δ cells. Gnant *et al* reported that combination therapy with hormone and bisphosphonate (zoledronate) preparations as post-operative adjuvant therapy for breast cancer in pre-menopausal women prolonged the relapse-free survival time compared to hormonal therapy alone (4,5). Many studies are currently being conducted to confirm the possibility that bisphosphonates contribute to prolonged survival.

In 2007, an oral radiation agent containing strontium-89 (Sr-89) was approved as a commercially available new drug for the treatment of bone metastasis in Japan. Sr-89 is recognized as an agent that relieves radiation-induced pain, as demonstrated in cases of external irradiation. This agent reaches metastatic bone sites throughout the whole body when intravenously

Table I. Efficacy studies involving single-dosage treatment with Sr-89 chloride.[a]

Author	Year	No. of patients	Cancer type	Radiation dosage	Response rate
Buchali	1988	41	Prostate	3x75 MBq	37
Robinson	1989	128	Prostate, breast	40 microCi/kg	80-89
Lewington	1991	26	Prostate	150 MBq	67
Laing	1991	83	Prostate	1.5-3.0 MBq	75
Haesner	1992	200	Prostate	3x37, 3x75 MBq	59
Quilty	1994	123	Prostate	200 MBq	65-70
Pons	1997	76	Prostate, breast	148 MBq	89-92
Baziotis	1998	64	Breast	2 MBq/kg	81
Kasalicky	1998	118	Prostate, breast	148 MBq	96
Fuster	2000	40	Breast	148 MBq	92
Kraeber-Bodere	2000	94	Prostate	150 MBq	60
Dafemou	2001	527	Prostate	148 MBq	60
Turner	2001	93	Prostate	150 MBq	63

[a]Adapted and modified from Lam *et al* (25). Response rate: percenatge of patients reporting either complete or partial pain relief.

administered as a single dose, and is therefore often employed to treat multiple bone metastases (Table I). However, an adverse effect of Sr-89 is that it induces bone marrow suppression, and the guidelines established in the US (6) and Europe (7) emphasize that physicians must carefully consider the use of chemotherapeutic agents and external irradiation in relation to the development and treatment of metastatic bone pain. However, there are no restrictions regarding combinations, such as with endocrine therapy, analgesic agents or adjuvant analgesic agents (e.g., bisphosphonates).

Few studies have reported the combination of bisphosphonates and Sr-89. Storto *et al* (8) reported that combination therapy with these two agents more effectively relieved pain than a single agent alone (Fig. 1). However, in their administration schedule, the simultaneous administration of the two agents was not employed. Sr-89 was gradually administered after a 6-month pre-treatment period with zoledronic acid alone, that is, Storto *et al* did not examine Sr-89 administration under continuous therapy with zoledronic acid. In a previous clinical trial involving Sr-89 in Japan (9), the effects of the combination therapy of this radiopharmaceutical with zoledronic acid on treatment efficacy was not considered. Thus, the efficacy and safety of simultaneous combination therapy with Sr-89 and zoledronic acid in Japanese patients remain to be verified.

In this study, Sr-89 was administered to breast cancer patients with painful bone metastasis who had continuously received zoledronic acid in our hospital and to those previously treated with an initial dose of zoledronic acid in order to evaluate the efficacy and safety of combination therapy with Sr-89 and zoledronic acid.

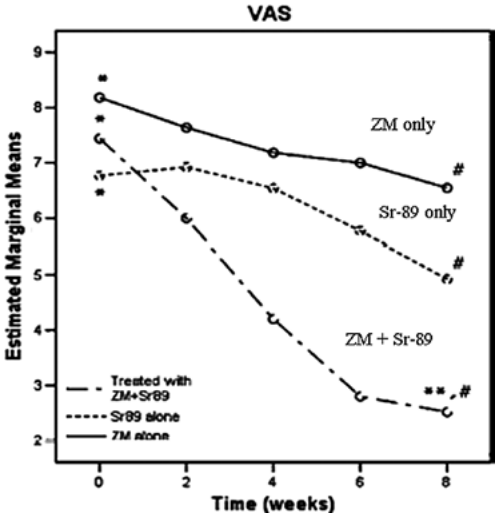

Figure 1. Improvement in reported pain scores according to the diaries of patients treated with combined therapy (ZM + Sr-89). VAS, visual analogue scale; ZM, zoledronic acid; *P=0.10 across categories at baseline; **P<0.01 for ZM + Sr-89 vs. both Sr-89 and ZM; #P<0.0001 vs. baseline for each group.

Materials and methods

The subjects were 16 breast cancer patients with painful bone metastasis in whom Sr-89 was added to zoledronic acid continuous therapy, or was added after an initial administration of zoledronic acid at the Department of Radiology in our hospital, between March 2007 and February 2011. We intravenously administered Sr-89 at a dose of 2 MBq/kg to a maximum dose of 141 MBq per person. Written informed consent was obtained from the patients before the study.

To assess treatment efficacy, patients who did not require an analgesic agent after Sr-89 administration because of the complete relief of pain were regarded as having achieved a complete response (CR). Those in whom the doses of analgesic agents, such as opioids and NSAIDs, could be decreased were regarded as having achieved a partial response (PR). Those in whom there were no changes in the doses of analgesic agents were regarded as showing no change (NC). Those in whom the doses of analgesic agents were increased were regarded as non-responders (NRs). After Sr-89 administration, brems-

Table II. Patients with painful bone metastasis from breast cancer (n=16).

Case no.	Age (years)	ZOL periods (months)[a]	Patient relief	WBC (x1,000)	Blood platelets (x10,000)	Radiation history	Pre-/during/ post-therapy	Survival period (months)[b]	Metastatic organs (except bone)
1	50	10	CR	7.1→5.0	22.4→18.3	+	**PTX-CBDCA/AI, H/**	2 M death	Lung
2	48	46	PR	5.0→	19.1→22.7	+	**TAM, PTX-H, VNB-H**//	10 M	Lung, liver
3	59	20	PR	3.8→5.7	20.1→19.4	+	/**AI**/	10 M death	ONJ
4	51	62	NC	4.1→2.8	18.6→20.0	+	ECT, CEF, T/**AI**/VNB	24 M death	Lung, liver
5	57	34	PR	3.5→1.9	15.5→18.5	+	XC, DTX/**AI/VNB**	20 M death	Liver
6	60	10	PR	6.9→7.4	20.0→24.7	+	EC-HT/**H, AI**/X	7 M death	Contra-breast, liver, adrenal
7	66	0	CR	7.9→7.5	19.5→15.1	-	/**AI**/	2 M death	Lung, liver, lymph node
8	50	8	PR	3.3→	23.3→	-	EC-wPTX/**TOR**/	5 M death	Liver, ovary, lymph node
9	53	12	PR	6.1→2.3	22.9→12.7	-	/**X**/GEM-VNB	2 M death	Liver
10	75	1	PR	8.6→	29.6→22.7	-	**AI**	12 M death	Bile pleural effusion
11	49	1	CR	5.2→2.4	46.0→20.9	-	/**GEM+VNB**	5 M	Liver
12	52	49	PR	4.5→3.1	21.6→17.3	-	**AI**	5 M	None
13	47	2	NC	4.0→3.7	31.2→13.7	-	**AI**/GEM+VNB	4 M	Liver, pancreas, bile pleural effusion
14	46	0	CR	5.3→2.9	20.0→14.5	-	**TAM**	3 M	None
15	39	0	CR	7.7→5.8	47.7→25.7	-	**TAM+LH-RH agonist**	2 M	Lung, pleural effusion
16	72	38	PR	5.3→5.0	16.3→15.0	-	AI/AI+XC/**TOR**/AI+5FU	2 M	Lung

[a]ZOL, administration months before Sr-89 administration; [b]survival in months after Sr-89 administration; ONJ, osteonecrosis of the jaw. PR, partial response; CR, complete response; NC, no change; PTX, paclitaxel; DTX, docetaxel; CBDCA, carboplatin; VNB, vinorelbine; GEM, gemcitabine; X, capecitabine; E, epirubicin; C, cyclophosphamide; F, fluorouracil; H, trastuzumab; AI, aromatase inhibitors; TAM, tamoxifen; TOR, toremifene; LH-RH, luteinizing hormone-releasing hormone. Bold indicates the cancer therapy performed when each patient was administered SR-89.

strahlung imaging in which Sr-89 β-ray damping radiation was visualized, which reflected the distribution of Sr-89, was performed to investigate the distribution of Sr-89 and compare it with ^{99m}Tc accumulation on bone scintigraphy.

To evaluate safety, we examined bone marrow toxicity and confirmed the minimum leukocyte and platelet counts during the 2 months after administration. The results were evaluated according to the Common Term Criteria for Adverse Events (v. 3.0).

Results

The characteristics of the 16 breast cancer patients with painful bone metastasis in this study are presented in Table II. CR was achieved in 5 patients, PR was observed in 9 and NC in 2 patients. In this study, pain relief was achieved in 14 of the 16 patients, indicating the efficacy of this combination. These effects appeared from 1 week to 1 month after administration.

With respect to safety, neither grade 3 or higher leukopenia nor thrombopenia was observed; the tolerance to adverse events was favorable.

Bone scintigraphy and bremsstrahlung imaging were performed. The accumulation of bremsstrahlung was consistent with the ^{99m}Tc uptake on bone scintigraphy in responders. However, only slight accumulation was noted in NRs (Fig. 2).

Discussion

We set out to investigate the efficacy and safety of combination therapy with zoledronic acid and Sr-89 for painful bone metastases from breast cancer.

When evaluating the efficacy of this combination with respect to changes in the doses of analgesic agents, 14 (88%) of the 16 patients responded to this therapy. Storto *et al* (8) examined patients with bone metastasis from prostate or breast cancer, and reported that 96% of patients after 6 months

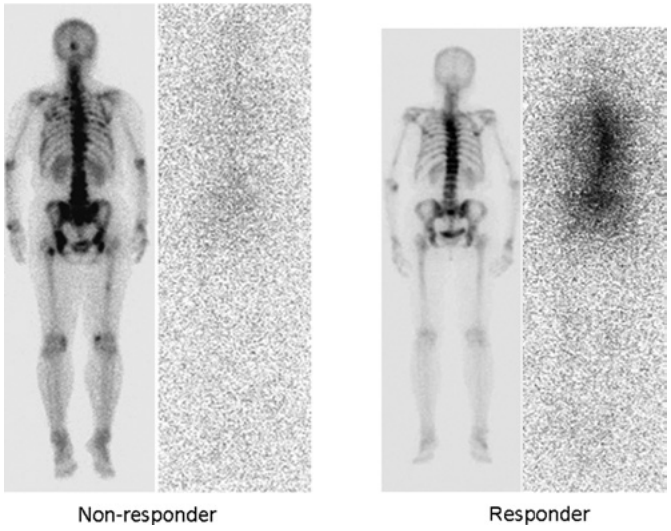

Figure 2. Bone scintigraphy and bremsstrahlung imaging.

of therapy with zoledronic acid responded to Sr-89 upon sequential administration, whereas the response rate was 82% in patients treated with Sr-89 alone. Furthermore, Finlay *et al* (10) in their systematic review indicated that the response rate for Sr-89 alone was 76%. The response rate of 88% under the combination therapy with zoledronic acid obtained in this study may not be significantly different to that reported by Storto *et al*.

Furthermore, bremsstrahlung imaging was performed with β-rays from Sr-89. As Sr-89 does not radiate γ-rays, it is usually difficult to visualize. However, bremsstrahlung radiation from β-rays partially facilitates the visualization of Sr-89 distribution, although the clarity is less marked than that of bone scintigraphy (11). As Sr-89 accumulation can be directly confirmed, we added this procedure to the efficacy assessment in this study. In breast cancer patients, Baziotis *et al* (12) reported a correlation between bremsstrahlung imaging findings after Sr-89 administration in breast cancer patients with bone metastasis and bone scintigraphy findings. In the present study, responders showed Sr-89 accumulation, which was consistent with the accumulation sites seen on bone scintigraphy. However, among NRs there was no Sr-89 accumulation, suggesting an association between efficacy and Sr-89 accumulation. According to Storto *et al* (8), combination therapy with zoledronic acid and Sr-89 may increase Sr-89 accumulation. This may contribute to the combination-related enhancement of the effects. In the present study, combination therapy with zoledronic acid and Sr-89 was also effective, but 1 patient showed only low-level Sr-89 accumulation under treatment with zoledronic acid, which had been administered over 62 months. It is known that zoledronic acid reduces osteolytic actions through osteoclast suppression. This may partially increase osteopoietic actions and promote Sr-89 uptake. However, the effect of long-term therapy with zoledronic acid on bone metabolism and Sr-89 accumulation remains to be clarified. Further investigation is required.

Concerning safety, bone marrow suppression related to Sr-89 administration under treatment with zoledronic acid was observed as grade 2 or lower leukopenia or thrombopenia. There were no grade 3 or higher adverse events. Storto *et al* reported that in a combination therapy (zoledronic acid + Sr-89) group, bone marrow suppression was slightly more marked than in an Sr-89 group. However, no patient required treatment. In the present study, bone marrow suppression associated with combination therapy with zoledronic acid and Sr-89 was tolerable, similar to that described by Storto *et al* (8).

In a clinical trial of Sr-89 in Japan, bone marrow suppression resulting in leukopenia and thrombopenia gradually appeared after Sr-89 administration and reached a peak 8 weeks after administration, before gradually returning to the baseline. Therefore, caution is required regarding combination therapy with chemotherapeutic agents, since bone marrow suppression may be enhanced. In established guidelines in Europe and the United States, it is recommended that combination therapy should be avoided for 3 months after Sr-89 administration. However, with respect to the combination therapy of Sr-89 and chemotherapeutic agents, few studies have examined the relationship between the timing of administration and tolerance. Most studies regarding Sr-89 involved patients who had received chemotherapy before Sr-89 administration, presenting it as a background factor. Akerley *et al* (13), Tu *et al* (14) and Sciuto *et al* (15) reported simultaneous combination therapy with Sr-89 and chemotherapeutic agents in patients with prostate cancer and observed tolerance. Furthermore, Tu *et al* (16) and Porfini *et al* (17) investigated whether or not chemotherapy can be performed after Sr-89 administration in prostate cancer patients, and concluded that chemotherapy was possible. To the best of our knowledge, no study of this combination in breast cancer patients alone has been reported in the literature.

In this study, we also reviewed chemotherapeutic regimens combined before and after Sr-89 administration. Chemotherapy with taxans or binorerbin, which may cause bone marrow suppression, was performed before Sr-89 administration in 7 of 16 patients treated with Sr-89: 2 patients during and 7 patients after administration. Bone marrow suppression was tolerable, suggesting that simultaneous combination therapy with chemotherapy before or after Sr-89 administration, or combination therapy early after administration is possible in patients with bone metastasis from breast cancer.

In Sr-89 administration, bone marrow function (as indicated by blood count values) must be maintained. When chemotherapy has been administered before Sr-89, Sr-89 treatment should be conducted after confirming recovery of blood count values. When administering chemotherapy after Sr-89 administration, physicians should confirm the reduction of Sr-89-related bone marrow suppression or recovery and tolerance to chemotherapeutic agents.

In this study, 8 of the 16 patients had undergone external irradiation. The mean and maximum tissue tracks of β-rays emitted from Sr-89 were 2.4 and 8 mm, respectively. Even if β-rays accumulate in vertebral bone metastatic sites, they may not reach the intramedullary space. Therefore, when additional external irradiation is not possible owing to the total dose reaching the tolerance level, Sr-89 therapy remains possible. However, combination therapy with external irradiation and Sr-89 should be carefully performed, since it may promote bone marrow suppression as an adverse effect. In the guidelines established in Europe and the US, it is stated

that combination therapy with half-body irradiation within 2-3 months should be avoided, whereas the combination of topical irradiation and Sr-89 is possible. In the present study, all subjects had also undergone topical external irradiation. Nevertheless, the results confirmed the efficacy and safety of Sr-89 therapy.

In the present study, the survival time after Sr-89 administration varied among the 14 responders (14/16), from 2 to 23 months or more (all responders succumbed to their primary disease). Several studies indicated that Sr-89 was effective in patients when administered in the early stage as an efficacy-predicting factor, whereas Sr-89 was less effective in the terminal stage and caused marked adverse effects (18-22). Therefore, when life expectancy is estimated to be extremely short (1 month or less), Sr-89 administration is not indicated. On the other hand, pain-removing effects may also be achieved in advanced cancer patients. Although it is difficult to accurately predict the effects of Sr-89 before treatment (23,24), we cannot deny its usefulness in terminal cancer patients. The results of this study showed the efficacy of Sr-89 regardless of life expectancy (2-23 months). When Sr-89 is indicated, early treatment should be positively considered. Even in terminal cancer patients, Sr-89 therapy may be a treatment option.

In conclusion, in this study pain-relief effects were achieved in 14 of 16 patients, suggesting the efficacy of combination therapy with zoledronic acid and Sr-89. Furthermore, there were no serious adverse events related to this therapy, and drug tolerance was favorable.

This combination therapy can be combined with endocrine and molecule-targeting therapies. In certain patients, combination therapy with chemotherapeutic agents was also possible. This combination therapy was safe and effective in patients with a history of external irradiation. As the use of Sr-89 may relieve pain and improve QOL, treatment with Sr-89 at the early stage, when its effects are more potent, should be considered in the future, and a large-scale clinical study should be conducted.

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