CASE REPORT

Radium-223 dichloride therapy in breast cancer with osseous metastases

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Accepted 31 October 2015

SUMMARY

Osseous metastases occur frequently in patients with breast cancer. Few options exist for bone targeted therapy for hormone refractory patients with breast cancer with progressive bone metastases. We present a case of breast cancer with osseous metastases but no visceral metastases. The patient had been treated with surgery, chemotherapy, radiation and hormonal therapy, but still had extensive symptomatic osseous metastases. She received radium-223 dichloride, a therapeutic radiopharmaceutical Food and Drug Administration (FDA) approved for castration resistant prostate cancer with bone metastases. She tolerated the therapy well with no significant adverse effects. She had an excellent response with significant pain relief obviating need for regular analgaesics. Her tumour markers also dropped significantly. Osseous metastases assessed with F-18 fluorodeoxy glucose (FDG) positron emission tomography/CT (PET/CT) and F-18 sodium fluoride (NaF) bone PET/CT scans at baseline, after two and six cycles, also showed interval improvement in the lesions. Radium-223 dichloride could potentially be a safe and useful therapeutic option in this setting.

BACKGROUND

Radium-223 dichloride (Ra-223) has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of castration resistant patients with prostate cancer with bone predominant metastases.¹ Since patients with breast cancer frequently have osseous metastases (similar to patients with prostate cancer), clinical trials are being planned to assess the use of Ra-223 therapy in patients with breast cancer with bone metastases alone.² The literature on use of Ra-223 for breast cancer with osseous metastases is very sparse. We previously reported the preliminary results of the Ra-223 experience in this patient and we now report the final report of our analysis. Our case report detailing our experience in this clinical setting would be a valuable addition to the literature. Another factor relevant in this setting is the lack of definite information about the changes in the osseous lesions with Ra-223 treatment on imaging follow-up (since the pre-FDA approval clinical trials evaluating the use of Ra-223 in metastatic prostate cancer did not involve dedicated imaging). Our patient was assessed using F-18 fluorodeoxy glucose (FDG) positron emission tomography/CT (PET/CT) as well as F-18 sodium fluoride (NaF) bone PET/CT scans to assess the impact of Ra-223 therapy on the osseous lesions. Our report can thus provide insights about the

appropriate imaging modalities to follow-up these lesions when patients are treated with Ra-223.

CASE PRESENTATION

A Caucasian woman, now in her late 60s, with a medical history significant for hypertension, hypercholesterolaemia, hypothyroidism, renal stones, rheumatoid arthritis and anxiety, as well as breast cancer initially diagnosed approximately 21 years prior, presented with increasing bone pain. She had oestrogen receptor positive, BRCA1/ BRCA2 negative, HER2/Neu negative, right breast cancer with nodal (8 of 16 ipsilateral axillary nodes) and bone metastases. After undergoing right mastectomy and right axillary nodal dissection, she received chemotherapy with doxorubicin, 5-fluorouracil, methotrexate and cyclophosphamide for 9 months, followed by hormonal therapy with oral tamoxifen for 4 year and 6 months. She did relatively well for approximately 10 years, after which she developed back pain and was treated for 5 weeks with directed radiation treatment to osseous metastatic disease in T-11 vertebra noted on MRI, followed by letrozole, an oral non-steroidal aromatase inhibitor, along with zoledronic acid for 2 years. Approximately 4 years later, her tumour marker cancer antigen 27.29 (CA 27.29) was elevated to 76 U/mL (normal range: <38 U/mL). MRI and CT scan revealed progressive disease involving the spine. Oral letrozole was changed to fulvestrant (a selective oestrogen receptor down-regulator) along with zoledronic acid. Her CA 27.29 levels decreased to within normal range. Progesterone cream was subsequently added to the regimen after a few months when her cancer markers started rising again. She continued on hormonal therapy for about 6 years, when she again developed significant pain; work up revealed progressive osseous metastatic disease. She was started on systemic therapy with the mammalian target of rapamycin inhibitor everolimus in combination with exemestane. She received only three cycles, at the starting dose of 2.5 mg orally every day. The 6-week therapy was complicated by shingles and abnormal liver function test studies, and CA 27.29 levels markedly increased to 705 U/mL. She also received spot radiation therapy to her shoulder, spine and hip regions. A subsequent CT scan showed no visceral metastatic disease; stable osseous metastatic disease in the spine correlated with progressive bone pain affecting the back, shoulder and pelvic regions.

The patient was referred to an advanced cancer treatment facility for consideration of molecular targeted therapy or clinical trials.

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To cite: Takalkar A, Paryani B, Adams S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211152

INVESTIGATIONS

1. Pathology review and Genomic analysis: Review of pathology showed spinal tumour cells to be strongly positive for oestrogen receptor (90%) and progesterone receptor (15%), but HER2 Neu gene amplification was equivocal (according to fluorescence in situ hybridisation score of 1.83). The immunohistochemical profile was consistent with breast tumour origin. *PIK3CA* mutation was detected in codon 1047, exon 21 (CAT to CGT), which would change the amino acid histidine to arginine. Although some clinical trials were available targeting the *PIK3CA* pathway, the patient was, unfortunately, not a candidate for any of them because she had no RECIST measurable disease.
2. An 18F-FDG PET/CT scan and 18F-NaF bone PET/CT imaging were carried out before, during and after therapy.
3. Tumour markers: CA 27.29 and serum alkaline phosphate.
4. Blood counts: Haemoglobin, platelets and absolute neutrophil count every month and post-therapy.

TREATMENT

Therapy with bone targeted agents such as Ra-223 was recommended. Ra-223 has been approved for castration resistant metastatic patients with prostate cancer with osseous metastases.¹ In this setting, Ra-223 has a survival advantage as well as symptomatic improvement with pain relief.³ Ra-223 is a calcium mimetic and localises to the sites of osteoblastic metastases and induces cell death by causing double stranded DNA break by virtue of α -particle release. Although not yet approved for patients with breast cancer, it can be postulated that metastatic breast cancer with osteoblastic metastases has a similar disease profile and can be expected to benefit from Ra-223 therapy. There have been some preliminary studies evaluating the safety and efficacy of Ra-223 in the setting of breast cancer.³ These studies and any safety data about Ra-223 in the setting of metastatic breast cancer were obtained from the manufacturer. The patient was counselled about various treatment options available to her, including additional chemotherapy, bone palliation with samarium-153 ethylene-diamine-tetra-methylene-phosphonic acid (Sm-153 EDTMP) or strontium-89 chloride (Sr-89) and supportive care. After weighing the risks versus benefits, an informed decision was made by the patient to pursue Ra-223 therapy (on an off-label basis). We again confirmed active osseous metastatic disease without any visceral metastatic disease by carrying out a baseline 18F-FDG PET/CT scan and 18F-NaF bone PET/CT imaging prior to Ra 223 dichloride therapy. Laboratory evaluation with complete blood count and chemistry profile was also performed to ensure patient eligibility for Ra-223 therapy. Her Eastern co-operative oncology group (ECOG) Performance status (PS) was 1. After the patient provided informed consent for the off label use of Ra-223, considering all the risks and benefits, she was treated with Ra-223 at a dose of 50 KBq/kg (or 1.35 μ Ci/kg) every 4 weeks for six cycles. Before each treatment, laboratory evaluation was performed to assess haematological parameters as well as cancer markers (CA 27.29 and serum alkaline phosphate). She completed all the six cycles without any interruption and with no adverse events. After treatment cycle 2 and cycle 6, 18F-FDG PET/CT and 18F-NaF bone PET/CT imaging studies were performed to evaluate the disease status on imaging.

OUTCOME AND FOLLOW-UP

The patient tolerated the therapy well and reported no significant adverse symptoms. Laboratory evaluation revealed no significant haematological toxicity (table 1). Haemoglobin and

Table 1 Blood count values during Ra-223 therapy

	Haemoglobin (g/dL)	Platelets ($\times 10^9$ /L)	ANC ($\times 10^9$ /L)
Cycle 1	12.9	246	3.3
Cycle 2	12.6	219	1.7
Cycle 3	12.7	217	1.5
Cycle 4	12.3	256	2.9
Cycle 5	13	207	2.0
Cycle 6	12.4	217	1.5
Postcompletion	12.0	220	1.9

ANC, absolute neutrophil count.

platelet count remained relatively stable throughout the course of therapy. Absolute neutrophil count did decrease but remained above the threshold, allowing the patient to continue receiving Ra-223 treatment; the patient did not develop any febrile neutropaenia.

The patient reported significant improvement in her pain, even after the first treatment, but more significantly after the third treatment. There was incremental and sustained improvement after each cycle. She was pain free without need for analgesics after cycle 3, and had sustained pain relief subsequently, with a very good quality of life and no restrictions in her daily activities (Eastern Cooperative Oncologic Group score of 0). Review of the pain assessment during clinical evaluation every month showed a decline from 8/10 pain to 1/10 pain. The pain relief lasted approximately 11 months postcompletion of therapy. Correlating with her symptomatic improvement, CA 27.29 as well as serum alkaline phosphatase (ALP) levels dropped with Ra-223 therapy (table 2 and graphs 1 and 2). CA 27.29 was 957.6 U/mL at baseline and dropped to 394.8 U/mL postcompletion of Ra-223 therapy. ALP was 134 U/L at baseline and dropped to 64 U/L postcompletion of Ra-223 therapy.

The osseous lesions also improved on imaging with Ra-223 therapy. We evaluated osseous disease with F-18 FDG PET/CT and F-18 NaF bone PET/CT scans by comparing baseline scans before therapy with the scans after cycle two and cycle six of therapy. Compared to baseline studies before the first treatment, scans (F-18 FDG PET/CT and F-18 NaF bone PET/CT) after completion of therapy showed significant interval improvement in the osseous lesions, more so with FDG PET/CT imaging. Although there was not complete resolution of all the lesions on either the F-18 FDG PET/CT or F-18 NaF bone PET/CT scans, many lesions showed improvement in size as well as intensity, and some lesions had resolved completely and became more sclerotic (especially on F-18 FDG PET/CT scans indicating treated inactive lesions). More lesions showed residual uptake on the post-treatment F-18 NaF bone PET/CT scan compared

Table 2 Tumor marker profiles during Ra-223 therapy

	CA 27.29 (U/mL)	ALP (U/L)
Cycle 1	957.6	134
Cycle 2	907.7	128
Cycle 3	837.4	137
Cycle 4	545.9	110
Cycle 5	551.9	89
Cycle 6	393.8	64
Postcompletion	394.8	65

ALP, alkaline phosphatase; CA, 27.29, cancer antigen 27.29.

to on the FDG PET/CT scan. The NaF bone PET/CT scan after the second treatment revealed more intense uptake in several lesions but the patient actually reported symptomatic improvement. These lesions improved on the NaF bone PET/CT scan after completion of treatment, suggesting the possibility of a 'flare' phenomenon after initiation of the treatment. For objective analysis of the scans, three well-defined discrete index lesions were selected on the baseline scans and followed on subsequent scans as regards their intensity of FDG or NaF uptake measured as the standardised uptake value (SUV)) and density on the CT portion of the study measured as Hounsfield units (HU) (tables 3 and 4).

All index lesions showed improvement (decrease in intensity of FDG or NaF uptake and increase in density on CT) from baseline scan to post-therapy scan (figure 1A, B). A lesion in L-2 vertebral body (which was intense on both F-18 FDG as well as F-18 NaF bone PET/CT scans) had SUVmax of 9.8 and 73.5, and HUavg of 267 and 253 on F-18 FDG and F-18 NaF bone PET/CT scans, respectively, before the initiation of Ra-223 therapy. The SUVmax decreased to 3.8 and 44 on F-18 FDG, and F-18 NaF bone PET/CT scans, respectively, and HUavg increased to 511 and 491 on F-18 FDG, and F-18 NaF bone PET/CT scans, respectively, after completion of Ra-223 therapy (figures 2A, B and 3A, B). The decrease in intensity of radiotracer uptake and increase in density of the lesions indicates that the lesion was becoming less active and more sclerotic, indicating response to treatment. The patient's ECOG PS, after all doses of Radium 223 were completed, improved to 0 from 1 before Ra-223.

DISCUSSION

This clinical case report describes a patient with hormone refractory breast cancer with osseous metastatic disease and no visceral metastases, treated with Ra-223 therapy. What is novel in this case is the decline in tumour markers. We had previously presented on this when the patient was undergoing but had not completed her therapy.⁴ This case report is the complete report on the patient's Ra-223 therapy, including completion of all six cycles, as well as the post-treatment imaging. Ra-223 has been approved only for metastatic castration resistant patients with prostate cancer with osseous metastases. The decision to treat this patient off-label was made on the basis of prior experience with Ra-223 in the setting of metastatic prostate with osseous metastases, and also based on preclinical and clinical research studies documenting the safety and potential efficacy of Ra-223 in the setting of osseous metastases from breast cancer. A pre-clinical study evaluated the use of Ra-223 in a mouse model of breast cancer, and found extended survival with decreased tumour growth, and inhibited differentiation of osteoblasts and osteoclasts, supporting the development of Ra-223 for

Table 4 Sodium Fluoride (NaF) PET/CT activity before, during and after Ra-223 therapy

NaF bone PET/CT Scans Index Lesions	Baseline		After 2 cycles		After 6 cycles	
	SUVmax	HUavg	SUVmax	HUavg	SUVmax	HUavg
Rt Clavicle	41.1	393.3	39.9	427.7	27.0	552.6
L-2 Vertebra	73.5	253	96.2	332.9	44	491
Rt Acetabulum	63.4	257.6	59.6	334.6	44.2	417.2

NaF, Sodium Fluoride; HUavg, average Hounsfield Units; PET CT, positron emission tomography/CT; Rt, right; SUVmax, maximum standardised uptake value.

treatment of patients with breast cancer with or at risk of developing bone metastases.⁵ An open label, multicentre, single arm phase IIa clinical study included 23 patients with breast cancer with osseous metastases who had progressed on endocrine therapy and were treated with 50 KBq/kg Ra-223 every 4 weeks for four cycles.⁶ This study indicated that Ra-223 was targeting the areas of increased bone metabolism caused by bone metastases. The treatment was tolerated well with most adverse events in *Common Terminology Criteria for Adverse Events* (CTCAE) Grade 1 or 2 category. Myelotoxicity was less compared to

Figure 1 Maximum intensity projection (MIP) images in the coronal projection of sequential Food and Drug Administration (FDG) positron emission tomography/CT (PET/CT) (A) and F-18 sodium fluoride (NaF) bone PET/CT (B) scans carried out at baseline (left), after two cycles (middle) and after six cycles (right) of Ra-223 therapy in this patient with hormone resistant breast cancer with osseous metastases. There is multifocal intense osseous metastatic disease on the baseline scans that show improvement (but not complete resolution) on the post-treatment scan after six cycles of Ra-223. The improvement is more robust on F-18 fluorodeoxy glucose (FDG) PET/CT scans where improvement is also seen after two cycles of Ra-223 therapy. On the NaF bone PET/CT scans after two cycles, some lesions actually appeared more intense but eventually improved after six cycles, raising the possibility of an imaging 'flare' phenomenon. ALP, alkaline phosphatase; CA, cancer antigen.

Table 3 FDG PET/CT activity before, during and after Ra-223 therapy

FDG PET/CT Scans Index Lesions	Baseline		After 2 cycles		After 6 cycles	
	SUVmax	HUavg	SUVmax	HUavg	SUVmax	HUavg
T-10 Vertebra	9.3	509.4	8.6	500	7.4	442.5
L-2 Vertebra	9.8	267	8	363.5	3.8	511
Lf Prox Femur	12.4	142.1	11.7	176.5	11.7	270.7

FDG, F-18 fluorodeoxy glucose; HUavg, average Hounsfield Units; Lf Prox Femur, left proximal femur; PET CT, positron emission tomography/CT; SUVmax, maximum standardised uptake value.

Figure 2 Selected fused positron emission tomography/CT (PET/CT) (top) and CT (bottom) images in the transaxial plane at the level of L-2 vertebra showing an intense osseous lesion in the L-2 vertebral body (arrow) on F-18 fluorodeoxy glucose (FDG) PET/CT (A) and NaF bone PET/CT (B) scans performed sequentially at baseline (left), after two cycles (middle) and after six cycles (right) of Ra-223 therapy in this patient with hormone resistant breast cancer with osseous metastases. On FDG PET/CT scans, the lesions are seen to be less intense on the fused PET/CT images and more dense/sclerotic on the CT images, with only minimal residual FDG uptake on the post-treatment scan after six cycles of Ra-223 therapy. On NaF bone PET/CT scans, the lesion shows increasing sclerosis on the CT images after two and six cycles of Ra-223 therapy, but is more intense after two cycles (compared to the baseline scan) and eventually decreases in intensity on the post-treatment scan after six cycles of Ra-223 therapy, reinforcing the possibility of an imaging 'flare' phenomenon.

therapeutic β emitting radiopharmaceuticals such as SA-153 and Sr-89.

For patients with breast cancer with bone metastases, bisphosphonates (zoledronic acid) and RANK-L monoclonal antibody (denosumab) are the primary targeted therapies, in addition to systemic chemotherapy options. External beam radiation therapy (for fewer osseous lesions) as well as β particle therapies such as Sm-153 EDTMP (for multifocal osseous metastases) are palliative.⁷⁻¹¹ Our patient was treated with Ra-223 with symptomatic benefit similar (or better than) available palliative options and with the potential for improved survival. The patient tolerated the therapy well and had an excellent clinical response with significant pain relief and improved quality of life. The significant drop in cancer markers reinforced favourable response to the therapy and, finally, imaging confirmed response in the osseous lesions. Our patient experienced a relatively durable response, remaining pain free for at least 11 months after completion of therapy. Ra-223 is currently approved for use in patients with metastatic castration resistant prostate cancer with osseous metastases and no bone metastases. Clinical trials are underway to assess the value of Ra-223 therapy in patients with breast cancer with bone metastases and no visceral metastases.² Our case report supports this trial

suggesting that Ra-223 therapy could have a potential role in the treatment of hormone refractory patients with breast cancer with bone metastases.

We evaluated the osseous lesions using two different imaging modalities: FDG PET/CT scans that assess tumour glucose metabolism and NaF bone PET/CT scans that assess osteogenic activity in osseous lesions (similar to traditional radionuclide bone scans). Since both studies utilise CT imaging for attenuation correction and anatomic localisation, in addition to functional information, morphological changes in the lesions could also be assessed. In our patient, both imaging studies (FDG PET/CT and NaF bone PET/CT scans) confirmed extensive osseous metastases. However, there was some difference on a lesion-by-lesion basis, with some lesions active on FDG PET/CT scans alone and some lesions active on NaF bone PET/CT imaging alone. Some lesions were active on both the scans. After treatment, there was overall improvement in the osseous metastatic disease on both the scans. However, the degree of improvement was more significant on FDG PET/CT imaging compared to NaF bone PET/CT scans. Moreover, on the FDG PET/CT scan performed after two cycles of treatment, most lesions appeared improved. However, on the NaF bone PET/CT scan performed after two cycles, some lesions became more

Figure 3 Selected fused positron emission tomography/CT (PET/CT) (top) and CT (bottom) images in the transaxial plane at the level of L-2 vertebra showing an intense osseous lesion in the L-2 vertebral body (arrow) on F-18 fluorodeoxy glucose (FDG) PET/CT scans performed sequentially at baseline (left), after two cycles (middle) and after six cycles (right) of Ra-223 therapy in this patient with hormone resistant breast cancer with osseous metastases. (A) The lesion is seen to become less intense on the fused PET/CT images and more dense/sclerotic on the CT images with only minimal residual FDG uptake on the post-treatment scan after six cycles of Ra-223 therapy. (B) It is more intense after two cycles (compared to the baseline scan) and eventually decreases in intensity on the post-treatment scan after six cycles of Ra-223 therapy, reinforcing the possibility of an imaging 'flare' phenomenon.

intense but improved on the subsequent scan after six cycles of therapy. The lesions became more sclerotic with treatment on both the scans (including the NaF bone PET/CT scan performed after 2 cycles) and the patient had symptomatic pain relief as well. This suggests that the NaF bone PET/CT scan after two cycles may be prone for imaging 'flare' phenomenon (similar to radionuclide bone scans).¹²

The decrease in tumour marker CA27.29 is a novel finding. Other studies with Radium 223 have mainly focused on the bone turnover markers. The fact that a tumour marker is decreasing in addition to FDG PET/CT showing a metabolic decrease in activity shows that Radium 223 clearly has a direct tumour killing effect. This could be likely attributable to highly localised radiation dose from α -particles at the bone metastatic sites that have rapidly cycling neoplastic cells. This could be an exciting strategy in select cancers that metastasise to the bone to combine it with standard care chemotherapy agents to maximise the tumour kill. However, this should be viewed as a preliminary finding and hypothesis generating from a single case that needs to be tested prospectively in larger patient cohorts. Previous studies in prostate cancer bone metastases have revealed that Radium 223 showed responses in palliation of bone pain, positive effects on changes in bone ALP and improved survival with limited toxicity. In our patient, the improvement of bone strength at the site of a bone metastasis directly reflects a reduction in skeletal related events, in addition to reduced pain. This could be related to the reduction in bone turnover and normalisation of bone metabolism at the bone metastases. Moreover, as Radium 223 mimics calcium and the α emissions act over a short distance, limiting collateral tissue damage, the normal bone is spared from the DNA-damaging effects of radium 223. This could, in the long term, lead to reduction in skeletal-related events and related morbidity and mortality.

Our case also suggests that FDG PET/CT imaging may be a better imaging modality to assess disease status and treatment response in patients with breast cancer with osseous metastases being treated with Ra-223. Moreover, FDG PET/CT scan also has the additional advantage of allowing assessment of visceral metastases at the same time.

In conclusion, our case suggests that Ra-223 can be a potentially useful therapeutic option for hormone resistant patients

Learning points

- ▶ Radium-223 (Ra-223) dichloride, an α particle emitting therapeutic radiopharmaceutical, is an approved therapy for the treatment of metastatic castration-resistant prostate cancer with symptomatic osseous metastases but no visceral metastases, and provides improved survival.
- ▶ We used Ra-223 to successfully treat a hormone-refractory breast cancer patient with symptomatic osseous metastases but no visceral metastases, with excellent response and no significant toxicity.
- ▶ Clinical response was accompanied by a significant drop in cancer and bone turnover marker levels. Imaging results also confirmed improvement in osseous disease.
- ▶ Ra-223 can be safely administered in a patient with hormone-refractory breast cancer patient with bone metastases.
- ▶ There may be potential for imaging 'flare' phenomenon on F-18 sodium fluoride (NaF) bone positron emission tomography/CT (PET/CT) scans during the therapy, and FDG PET/CT scan may be a better imaging modality to assess disease status and treatment response.

with breast cancer with osseous metastases and no visceral metastases. Ra-223 therapy is usually well-tolerated but does require monitoring of haematological parameters. FDG PET/CT imaging may be an optimal imaging modality to assess disease status and treatment response along with clinical evaluation, ALP levels and cancer markers. Our report supports the planned clinical trial to assess the safety and efficacy of Ra-223 in this patient population.

Acknowledgements The authors thank the patient for consenting to this manuscript being written.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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