Case report

Ra223 in Bone Metastases with Osteolytic Activity

Renato Patrizio Costa, Davide Cardile, Alessandra Murabito, Vincenzo Tripoli, Francesco Verderame¹

Nuclear Medicine, Biomedical Department of Internal and Specialist Medicine, University of Palermo, ¹Department of Oncology, Villa Sofia-Cervello Hospital, Palermo, Italy

Abstract

Radium 223 dichloride (Ra223) is the only targeted alpha therapy able to extend survival in patients with bone metastases from prostate cancer. Mechanism of action and data currently available focused mainly on osteoblastic metastases from prostate cancer. In our institution, a patient with breast cancer affected by osteolytic metastases was treated with off-label use of Ra223. The evaluation of the deposit areas of Ra223 showed a perfect overlap with the regions of osteolysis previously detected by scintigraphy, indicating a possible therapeutic effect. This case report is the first document attesting Ra223 deposit in osteolytic metastases opening new opportunity of therapeutic development for this radiopharmaceutical.

Keywords: Bone metastases, breast cancer, osteoblastic bone metastases, osteolytic bone metastases, radium 223

Introduction

Among therapies available to manage bone metastases in patients with advanced stages of cancer, radium 223 dichloride (Ra223) (Xofigo injection, Bayer HealthCare Pharmaceuticals Inc.,) is the only targeted alpha therapy approved by health authorities to extend survival.^[1,2] This drug demonstrated to improve overall survival in a large Phase 3 trial conducted in males with castration-resistant prostate cancer (mCRPC), symptomatic bone metastases, and no visceral metastases.^[3]

Ra223 is a bone-seeking, α -emitting radionuclide which mimics calcium and emits high energy, the short range alpha-particles induces double-strand breaks in DNA, with a killing action on the surrounding cells.^[4]

The-decay process of Ra223 is accompanied by gamma emissions; this permits the use of a gamma camera scintigraphy to get quantitative imaging of the radiopharmaceutical with 30–60 min acquisition

Address for correspondence: Dr. Renato Patrizio Costa, Via Corradini Pietro Marcellino 3, Palermo, Italy. E-mail: renatopatrizio.costa@gmail.com

Access this article online
Quick Response Code:
Website:
www.wjnm.org
DOI:
10.4103/wjnm.WJNM_22_17

technetium-99 scans, confirming that Ra223 was localized in tissues of bone formation of osteoblastic bone metastases.^[6] Nowadays, literature data refer effectiveness of Ra223 mainly on tumors with bones osteoblastic activity, such

times.^[5] Using this technique, important biodistribution

studies discovered that the preferential uptake of Ra223

was overlapping with images previously detected by

as prostate cancer. Phase 1 and 2 trials documented a clinical efficacy also in breast cancer patients with predominately bone disease, highlighting a reduction in alkaline phosphatase and other bone biomarkers.^[6,7] Notwithstanding, studies are currently ongoing on tumors associated with mixed osteolytic/osteoblastic lesions.^[8]

To the best of our knowledge, here, we present the first evidence of a possible activity of Ra223 in osteolytic bone metastases arising from a patient with breast cancer.

Case Report

In June 2010, a caucasian 62-year-old woman afferred to our institution for a breast cancer on the left mammary region.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Costa RP, Cardile D, Murabito A, Tripoli V, Verderame F. Ra223 in bone metastases with osteolytic activity. World J Nucl Med 2018;17:116-9.

The patient was surgically treated with a Madden's mastectomy with ipsilateral axillary lymph node dissection; the diagnosis reported an invasive poorly differentiated ductal carcinoma staged as a Grade 3 disease. According to the tumor, node, metastasis staging system, the tumor was defined as pT4, pN2, and M0.

Pathological evaluation revealed that the tumor was positive for the hormone receptor (90% both for estrogen and progesterone) and classified as 2+ according to HER2 fluorescence *in situ* hybridization classification of breast cancers.

The proliferation marker Ki-67 resulted in 20%.

The patient received an adjuvant therapy based on six cycles of the two chemotherapeutic agents doxorubicin plus docetaxel (50 and 75 mg/m², respectively). Successively, a total of 18 Herceptin maintenance doses (6 mg/kg) were administered every 3 weeks.

The positivity of the estrogen receptor turned out to an additional adjuvant treatment with tamoxifen (20 mg/die) the subsequent 5 years.

The patient resulted clinically stable until September 2016, when she started to complain of pain in regions lower back, ribs, and right occipital.

The mammography on the right breast resulted negative, but levels of the serum tumor markers carcinoembryonic antigen (CEA) and CA15-3 suggested a possible breast cancer recurrence (CEA: 8.3 ng/ml, CA15-3: 41 U/ml).

The consequent computed tomography (CT) scans revealed a massive osteolytic area in the parietal-occipital and right occipital and the consequent disruption of cortical bone tissue [Figure 1]. In addition, nodular formation on the left chest wall associated with contrast enhancement was detected near the prosthesis. An abnormal single lymphnode was detected in the aortic arch area (2 cm).

In December 2016, a bone scan with ^{99m}TC-methylene diphosphonate discovered neoplastic bone secondarisms placed both in right parietal-occipital and median occipital [Figure 2]. Other disease localizations documented at bone scan were the right iliac crest, the right fourth costal arch, and the T12–L1 vertebral tract.

Because of the undoubted relapse of the disease, a combination strategy with trastuzumab-pertuzumab associated with docetaxel was proposed as first-line therapy.

Since the patient refused this treatment, an alternative was identified with the association between trastuzumab

(loading dose 8 mg/kg intravenous (IV), then 6 mg/kg IV every 21 days) and letrozole (2.5 mg/die).

Taking into account the bone prevalent disease, our multidisciplinary team evaluated a supplementary strategy with the addition of a possible bone-targeted agent targeting bone secondarisms. Additional goal was to select a therapy aiming to maintain the quality of life to avoid a new refuse of the patient for the therapy proposed.

Based on Phase 2 clinical data, we decided to propose the off-label use of the radiopharmaceutical Ra223.^[7]

The patient was instructed about the risks (as expected adverse events) and potential benefits of the therapy, the off-label use, as well as required precautions to be taken after Ra223 administration. A complete blood count and chemistry profile ensured that the patient was eligible for Ra223 therapy; subsequently, the agreement on informed consent for the off-label use was obtained.

Hospital administration approved the authorization for the off-label use of Ra223 at December 2016.

A total of four treatments were planned with a dose of 55 KBq/kg every 4 weeks according to Phase 2 data; the first administration of 5280 KBq of Ra223 was performed in January 2016.

Four days later, the patient was assessed with a planar whole-body scintillation γ -camera imaging.

(Ge Millennium MG, collimators LEGP, energy peak 82 kev + 154 kev, widht 20) to evaluate biodistribution of Ra223 and to gather planar imaging of skull, thorax, and pelvis.

Images showed the preferential uptake of Ra223 in gamma scintigrams overlapped the same osteolytic lesions previously identified by computed tomography (CT) and technetium-99 scans [Figure 3].

Discussion

Among the categories of cancer with probable diffusion to bone, breast cancer could represent an important achievement in the Ra223 developing program. Currently, two randomized Phase 2 studies are comparing this radiopharmaceutical with placebo in patients with bone predominant HER2-negative, hormone receptor-positive metastatic breast cancer, with the aim to evaluate the efficacy of the combination of the radiopharmaceutical with hormonal therapy or everolimus and extramestane (NCT02258451, NCT NCT02258464). However, the rationale to evaluate Ra223 in this pathology appears not solid as in mCRPC.^[9]

In fact, the current biological models set up to explain drug efficacy, contemplate that Ra223 is being incorporated in the high turnover areas of bone tissue, generally represented by bone metastases, approximately 2 h after injection.^[10] In these neoformation regions, Ra223 is able to replace calcium to hydroxyapatite crystals.^[11]

Consequently, the emission of potent doses of cytotoxic radiations to osteoblastic bone lesions induces the DNA double-strand break in the surrounding cancer cells and limits damage to adjacent bone marrow or to healthy tissue.

Based on this mechanism of action, Ra223 reveals a meaningful effectiveness on bone metastases with predominant osteoblastic activity. Conversely, the efficacy of the radiopharmaceutical on mixed or exclusively lytic metastases is still a gray area, in fact, authors report this issue as absolute contraindication to the use of the radiopharmaceutical.^[12]

Preclinical studies conducted in tumor-bearing mice model reported that Ra223 had reduced number of osteoclast and showed a dose-dependent inhibition of osteoclast differentiation without affecting the resorption activity of osteoclasts.^[13] Based on these evidence, authors reported that Ra223 uptake in the bone microenvironment surrounding metastatic foci is roughly the same in both osteolytic and osteoblastic tumors, but unfortunately, no robust confirm has been gathered in human studies.^[14,15]

At this regard, based on our knowledge, this case report is the first literature evidence showing a possible efficacy of the radiopharmaceutical on osteolytic bone metastases.

In breast cancer, bone is the most common site of metastatic recurrence, and only 15-20% show an osteoblastic activity.^[16]

In our patient, the images obtained from CT and bone scan collected before beginning Ra223 reported a bone metastatic disease with well-defined areas of osteolysis.

A subsequent analysis was conducted after Ra223 therapy using a gamma camera to reveal the deposit areas of the radiopharmaceutical.

The comparison of the images obtained by the three methodologies allowed to conclude that the deposit areas of Ra223 were perfectly overlapping with those previously observed by scintigraphy and CT.



Figure 1: Axial computed tomography image shows osteolytic metastases parietal-occipital right



Figure 2: Tc-99m hydroxydiphosphonate is in the bone surrounding the lytic lesion



Figure 3: The evaluation of the deposit areas of radium 223 showed a perfect overlap with the regions of osteolysis previously detected by scintigraphy

This could lead to theorize the possible clinical efficacy of Ra223 even in tumors with predominant osteolytic metastases, providing an important rationale to follow with attention the ongoing studies on bone disease arising from primary tumors of thyroid (NCT02390934) and kidney (NCT02406521). Finally, this activity on tumors with osteolytic metastases, if it would be confirmed, could generate new hopes of therapy for disease where Ra223 is yet to be tested as melanoma cancer^[17] and multiple myeloma.

Financial support and sponsorship Nil.

Conflicts of interest

The authors declare no conflicts of interest.

<u>References</u>

- Carroll PR, Parsons JK, Andriole G, Bahnson RR, Castle EP, Catalona WJ, et al. NCCN guidelines insights: Prostate cancer early detection, Version 2.2016. J Natl Compr Canc Netw 2016;14:509-19.
- AIOM 2016 Prostate Cancer Guidelines Downloadable. Available from: http://www.aiom.it/C_Common/Download. asp?file=/\$Site\$/files/doc/LG/2016_LG_AIOM_Prostata. pdf. [Last accessed on 2017 Feb 28].
- 3. Parker C, Sartor O. Radium-223 in prostate cancer. N Engl J Med 2013;369:1659-60.
- Carrasquillo JA, O'Donoghue JA, Pandit-Taskar N, Humm JL, Rathkopf DE, Slovin SF, et al. Phase I pharmacokinetic and biodistribution study with escalating doses of 223Ra-dichloride in men with castration-resistant metastatic prostate cancer. Eur J Nucl Med Mol Imaging 2013;40:1384-93.
- Hindorf C, Chittenden S, Aksnes AK, Parker C, Flux GD. Quantitative imaging of 223Ra-chloride (Alpharadin) for targeted alpha-emitting radionuclide therapy of bone metastases. Nucl Med Commun 2012;33:726-32.
- Nilsson S, Larsen RH, Fosså SD, Balteskard L, Borch KW, Westlin JE, et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. Clin Cancer Res 2005;11:4451-9.

- Coleman R, Aksnes AK, Naume B, Garcia C, Jerusalem G, Piccart M, *et al.* A phase IIa, nonrandomized study of radium-223 dichloride in advanced breast cancer patients with bone-dominant disease. Breast Cancer Res Treat 2014;145:411-8.
- 8. Nguyen NC, Shah M, Appleman LJ, Parikh R, Mountz JM. Radium-223 therapy for patients with metastatic castrate-resistant prostate cancer: An update on literature with case presentation. Int J Mol Imaging 2016;2016:2568031.
- 9. Effect of radium-223 on breast cancer bone metastases in mice. Bonekey Rep 2013;2:457.
- Yoshida K, Kaneta T, Takano S, Sugiura M, Kawano T, Hino A, et al. Pharmacokinetics of single dose radium-223 dichloride (BAY 88-8223) in Japanese patients with castration-resistant prostate cancer and bone metastases. Ann Nucl Med 2016;30:453-60.
- 11. Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, *et al.* Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: Results from a phase 3, double-blind, randomised trial. Lancet Oncol 2014;15:738-46.
- Borsò E, Boni G, Galli L, Ricci S, Farnesi A, Mazzarri S, et al. Radium 223 dichloride: A multidisciplinary approach to metastatic castration-resistant prostate cancer. Future Oncol 2015;11:323-31.
- 13. Suominen MI, Rissanen JP, Käkönen R, Fagerlund KM, Alhoniemi E, Mumberg D, *et al.* Survival benefit with radium-223 dichloride in a mouse model of breast cancer bone metastasis. J Natl Cancer Inst 2013;105:908-16.
- 14. Abou DS, Ulmert D, Doucet M, Hobbs RF, Riddle RC, Thorek DL. Whole-body and microenvironmental localization of radium-223 in naïve and mouse models of prostate cancer metastasis. J Natl Cancer Inst 2015;108. pii: Djv380.
- 15. Aprile C, Persico MG, Lodola L, Buroni FE. Radium-223 and metastatic castration-resistant prostate cancer: All that glitters is not gold. World J Radiol 2016;8:816-8.
- 16. Yin JJ, Pollock CB, Kelly K. Mechanisms of cancer metastasis to the bone. Cell Res 2005;15:57-62.
- 17. Silva SC, Wilson C, Woll PJ. Bone-targeted agents in the treatment of lung cancer. Ther Adv Med Oncol 2015;7:219-28.