Commentary

Therapeutic effect of RA223 in the management of breast cancer bone metastases

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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. 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. In our institution, a patient with breast cancer affected by osteolytic metastases was treated with off-label use of Ra223. Our patient had a good treatment compliance and up to now she has not been revealed the presence of SSE or hematological complications. Our preliminary experience shows that Ra223 may play a critical role to bone metastases in patients with breast cancer. Clin Ter 2019; 170(1):e1-3. doi: 10.7417/CT.2019.2100

Key words: Bone metastases, breast cancer, osteoblastic bone metastases, osteolytic bone metastases, radium 223

Introduction and background

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, alpha-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 times (5). Using this technique, important biodistribution studies discovered that the preferential uptake of Ra223 was overlapping with images previously detected by 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 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.

Our experience in bone metastases

In June 2010, a caucasian 62-year-old woman afferred to our institution for a breast cancer on the left mammary region. 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 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 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 (Fig. 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 lesions placed both in right parietal-occipital and median occipital (Fig. 2). Other disease localizations documented at bone scan were the right iliac crest, the right fourth costal arch, and the T12–L1 vertebral tract.

Since the patient refused any treatment and taking into account the bone disease, our multidisciplinary team evaluated a supplementary strategy with a possible bone-targeted agent targeting bone metastasis with Ra223. 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 six 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

Discussion

According to many studies, osteolytic metastases are able to uptake Radium-223 and so it was possible to complete the treatment cycles of bone metastases (one administration every 28 days for 6 cycles) obtaining the immediate resolution of the painful symptoms, but especially the almost resolution of skeletal metastatic lesions (Fig. 3).

In light of this study, it has been concluded that Radium-223 therapy is efficient on the patients performance status and overall survival and it could be used to patients with breast cancer bone metastases without known visceral metatases.

Since December 2016 to the present day, the patient has not manifested any particular symptoms during the follow-up.

Our preliminary experience shows that Ra223 may play a critical role to bone metastases in patients with breast cancer. Although a study with a higher number of patients is needed to assess the overall survival and the possible avise of hematological toxicity and SSE. It’s possible to say that our patient had a good treatment compliance and up to now she has not been revealed the presence of SSE or hematological complications. The loss of pain and the morphometabolic reduction in bone lesions demonstrate
that Radium 223 could be used for the treatment of bone metastases in patients with breast cancer.

Competing interests

The authors declare no competing and financial interests regarding this manuscript.

References