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CASE REPORT

^{223}Ra-dichloride therapy in an elderly bone metastatic castration-resistant prostate cancer patient: a case report presentation and comparison with existing literature

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Background

Prostate cancer (PC) is the most common male cancer and one of the leading causes of cancer-related morbidity and death. PC affects predominantly the elderly, the highest incidence rates being between the age of 70 and 80 years. Owing in part to the aging population and long natural history of the disease, approximately 54% of men who die of PC are older than 80 years of age. In the natural history of the disease, approximately 10% of patients will develop a castration-resistant prostate cancer (CRPC) which is characterized by a poor prognosis, with a median survival of 2 years. In a recent analysis on PC frequency in the elderly population, it has been shown that older patients are more likely to present with very advanced disease and to have a greater risk of death from PC than other competing causes [1]. The majority of patients with metastatic CRPC has a radiological evidence of bone metastases, which are cause of pain and disability, leading to a reduced quality of life. Moreover, bone metastases in patients with CRPC are independently associated with increased mortality. In consideration of the needs of older patient population, the optimal approach of elderly PC patients poses a particular clinical challenge.

Over last years, several novel drugs for CRPC have been introduced, such as the new taxan agent cabazitaxel, immunotherapy (sipuleucel-T), RANK-L inhibitor denosumab, androgen biosynthesis inhibitors (abiraterone acetate), and androgen receptor antagonists (enzalutamide). These antitumoral agents have changed therapeutic management of CRPC patients, although there is still the need to define an appropriate sequencing for their application to maximize patient benefit and minimize costs. In this evolving scenario, a first-in-class alpha-emitting radionuclide, ^{223}Ra-dichloride, has been recently approved for the treatment of CRPC patients with symptomatic bone metastases and no known visceral disease. FDA approval of ^{223}Ra came in May 2013 as a result of the findings of the international, randomized, double-blind alpharadin in symptomatic prostate cancer (ALSYMPCA) Phase III trial that evaluated efficacy on overall survival of ^{223}Ra treatment versus placebo in patients with mCRPC [2].

Thanks to its analogy to calcium, ^{223}Ra targets areas of high osteoblastic activity such as sites of bone metastases, delivering high-energy short-range alpha particle radiation. Alpha particles are characterized by a high-linear energy transfer (LET) to surrounding tissues delivered in a short path (<100 μm), inducing double-stranded breaks in DNA with a local cytotoxic effect that is, notably, independent from dose rate, oxygen level, and cell cycle status [3]. The short penetration range of alpha particles (approximately corresponding to 2–10 cell diameters) determines a low dose of radiation delivered to normal bone-marrow cell population, with minimal hematological adverse effects. Results

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of the ALSYMPCA trial have shown a significant impact of ^{223}Ra therapy on overall survival (OS) and a delay in median time to the first symptomatic skeletal event (SSE), associated with a relevant bone pain palliation. In addition, ^{223}Ra treatment was characterized by a low toxicity profile in terms of both hematologic and non-hematologic adverse events, which were mild to moderate in intensity. It is worth of note how the ALSYMPCA study population had a median age of 71 years, with 28% of the patients being ≥75 years.

The following case report describes the clinical management of a 91-year-old patient diagnosed with prostatic adenocarcinoma at the age of 86. By presenting this case, we wish to discuss the clinical management of very elderly CRPC patients taking into account the existing literature.

Case presentation

Our patient is a 91-year-old Caucasian male. At the age of 86, due to the evidence of a PSA level of 926 ng/ml, he underwent a transrectal ultrasound-guided biopsy of the prostate. He was diagnosed with a prostate adenocarcinoma Gleason score 7 (4 + 3). At that time (2011), his baseline ECOG Performance Status was 2.

A comprehensive geriatric assessment (CGA) was carried out by the means of activities of daily living (ADLs) and instrumental activities of daily living (IADLs) indexes and the vulnerable elders' survey-13 (VES-13) scoring system. The patient presented a condition of moderate functional dependence from caregivers, while VES-13 score evidenced a state of increased vulnerability (score = 6/10). Given the CGA and the high-risk of metastatic disease, he did not receive curative local external beam radiation therapy and was initiated on a combined androgen blockade (CAB) therapy with bicalutamide and LHRH agonist. Staging whole body CT scan did not show malignant lymphadenopathies or distant visceral disease. 99mTc-Dyphosphonate bone scan showed the presence of multiple areas of increased radiotracer uptake in the sternum, multiple costal arches, multiple vertebral bodies, and bone segments of the pelvis. In July 2012, PSA level reached a suboptimal nadir value of 4.17 ng/ml, also due to the fact that the patient did not appropriately assume CAB therapy. In May 2013, follow-up WB CT scan showed a significant progression of bone disease. Zoledronic acid treatment was started. In this period, he experienced the onset of bone pain in the sacral region (Brief Pain Inventory-Numeric Rating Scale BPI-NRS 7), so antalgic therapy with Acetaminophen was introduced. In February 2014, the patient underwent a low-dose docetaxel regimen, which was discontinued after the second cycle due to the evidence of a PSA level of 2.486 ng/ml. Consequently, abiraterone therapy was started.

As a result of the lack of therapeutic benefit from other treatments and due to the presence of painful bone metastases, the patient was proposed with ^{223}Ra-dichloride therapy. The patient was referred from medical oncologist to Nuclear Medicine Unit for ^{223}Ra therapy in August 2015, at the age of 90. At the first clinical evaluation, the patient presented with an ECOG Performance Status of 2 and moderate bone pain localized in lumbar and sacral region (BPI-NRS 6). antalgic therapy was based on acetaminophen (1 g twice a day).

Before each ^{223}Ra infusion, a complete hematologic profile, total Alkaline Phosphatase (t-ALP), and PSA levels were recorded. Pain score was evaluated with BPI-NRS 0–10. To assess quality-of-life (QoL) endpoints, the patient was asked to complete the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC QLQ-C30) and the bone metastasis module QLQ-BM22. Both were submitted at baseline and after every cycle of therapy.

A baseline bone scan was performed a month before the first ^{223}Ra injection. The patient presented multiple foci of increased radiotracer uptake localized in the sternum, right humeral head, multiple costal arches, and vertebral bodies, in the pelvis and in right femoral head. The patient underwent the first ^{223}Ra administration in September 2015. He reported a transient pain flare phenomenon few days after ^{223}Ra infusion, treated with Acetaminophen. From the second ^{223}Ra cycle on, the patient experienced a moderate response on bone pain without any reported gastrointestinal adverse effect.

During the course of treatment, progressive anemia was observed. After the fifth ^{223}Ra cycle, the patient underwent a blood transfusion, due to an Hb value of 6.5 gr/dl. The patient completed the sixth ^{223}Ra cycle in February 2016, without any particular gastrointestinal adverse effect and without experiencing further pain flare phenomenon. Pain scores recorded during the course of ^{223}Ra treatment are summarized in Fig. 1.

The first follow-up visit was performed a month after last ^{223}Ra cycle. PSA reached the value of 6711 ng/ml. Nevertheless, bone scan performed a month after last ^{223}Ra cycle reported stability of bone disease. Currently, his Performance Status is stable.

Conclusions

This case report presented a 91-year-old patient with bone metastatic CRPC treated with androgen-deprivation therapy, cytotoxic chemotherapy, abiraterone, and, finally, ^{223}Ra-dichloride.

The disease presented a very indolent trend over a period of 6 years. Initially, CAB provided a partial biochemical

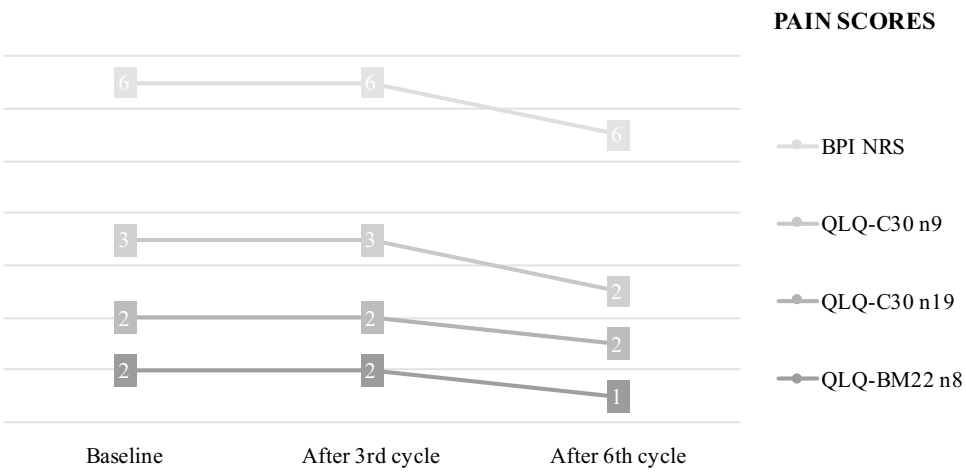

Fig. 1 Pain outcome during ^{223}Ra treatment

response; then, PSA presented a constant rising trend and bone imaging showed progression of skeletal disease despite cytotoxic chemotherapy and abiraterone regimen. ^{223}Ra-dichloride therapy provided control of bone metastatic disease over the 6-month treatment period. In our opinion, taking into account the optimal platelet count, the progressive anemia showed by the patient was reasonably due to the extent of bone disease than to ^{223}Ra hematologic toxicity, which is more often cause of trombocythopenia [2].

The optimal management of elderly patients affected by mCRPC poses a clinical concern, as it requires a careful assessment of several aspects associated with chronological age. This population is generally characterized by lower physiological reserves, a reduced functional status and related comorbidities. A comprehensive geriatric assessment is an essential diagnostic instrument designed to detect and evaluate multidimensional age-related issues, to plan appropriate interventions [4]. In elderly patients, in fact, polypharmaceutical regimens increase the risk of pharmacologic interactions and drug toxicity from the association with antineoplastic therapies. Moreover, because of adverse events, elderly patients often experience delays in anticancer treatments or dose reductions with a possible decrease in the efficacy of therapy, together with a lower treatment compliance.

Given the particular needs of elderly patients and the palliative nature of CRPC treatments, the recent approval of the alpha-emitter ^{223}Ra-dichloride therapy has introduced the possibility to delay SSE with no major concerns about drug-related toxicity and patients' compliance. A *post-hoc* analysis of ALSYMPCA patients stratified by age (<65 and > 65 years) demonstrated that ^{223}Radium prolonged survival and delayed time to first SSE in both younger and older patients, with a favorable safety profile. No analysis of the pivotal trial or Early Access Program has specifically investigated the clinical outcomes and safety profile of Radium-223 in the elderly. However, as Radium-223 treatment is characterized by low rates of hematological and nonhematological toxicities, it can be postulated that age does not affect its tolerability or efficacy.

Although the new-generation hormonal agents are easy to administer and better tolerated, it is necessary to remember that they are not devoid of side effects and also require careful management. ^{223}Radium is characterized by a reduced bone-marrow toxicity and a non-overlapping mechanism of action, thus permitting the combination with other therapeutic options for CRPC [5]. This radiopharmaceutical could be a safer therapeutic option in older patients too frail for cytotoxic chemotherapy or characterized by a delayed bone-marrow recovery after chemotherapy. Notably, there are no special precautions to be taken by patients' family members or caregivers even in patients with urinary incontinence, due to the very low renal excretion.

Literature data, to our knowledge, do not provide data focused on use of ^{223}Ra in very elderly subjects; in fact, in the fundamental ALSYMPCA trial, the study population had a median age of 71 years, with 28% of the patients being ≥75 years. However, this radiometabolic therapy seems generally well tolerated and does not interact with comedication, making it a good option in very elderly patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Written informed consent was obtained from the patient for publication of this case report.

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