Case Report

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Fatal Pancytopenia Associated with Radium-223 Dichloride in a Patient with Castration-Resistant Prostate Cancer and Multiple Bone Metastases

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ABSTRACT

Radium-223 dichloride (Ra-223) is an alpha-emitting radioisotope that targets osteoblastic metastasis of prostate cancer. For Ra-223, a favorable safety profile has been described. However, here we report a case of a fatal hematologic toxicity following the administration of Ra-223 observed at our hospital. An 80-year-old man with castration-resistant prostate cancer (CRPC) and multiple metastatic bone lesions was treated with Ra-223. He was complicated with systemic edema, constipation, and decline of renal function. One week later, he developed pancytopenia which deteriorated gradually, and died with severe prolonged pancytopenia and pneumonia 4 weeks after administration of Ra-223. Our report demonstrates the risk of fatal hematologic toxicity of Ra-223 even though pretreatment clinical and laboratory findings fulfill the selection criteria. Caution should be paid when prescribing Ra-223 to a patient with systemic edema, constipation, and decline of renal function.

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Introduction

Radium-223 dichloride (Ra-223) is an alpha-emitting radioisotope that targets osteoblastic metastasis of prostate cancer (castration-resistant prostate cancer or CRPC) (1, 2). Ra-223 can improve overall survival in patients with CRPC and bone metastases (1-3). However, hematopoietic toxicity among patients with high skeletal tumor burden has been reported (4). In the ALSYMPCA trial, grade 4 anemia, neutropenia, and thrombocytopenia were observed in 2%, 1%, and 3%, respectively (2). However, severe hematologic toxicity is rare.

To the best knowledge of the authors, only one grade-5 hematologic adverse event has been reported so far (2). Here, we report another case of fatal hematologic toxicity presumably induced by Ra-223.

Case Report

An 80-year-old man with CRPC was referred to our department for treatment of bone metastases with Ra-223. He had been diagnosed with metastatic prostate cancer at a different institution 2 years before. His Gleason score was 9 (4 + 5) on biopsy and the initial prostate-specific antigen (PSA) level was 479.5 ng/ml. Whole-body bone scintigraphy demonstrated multiple metastasis throughout the skeleton. The computed tomography (CT) scan revealed no metastasis to lymph nodes or other organs, but urinary bladder invasion was detected by cystoscopy.

The patient was referred to our department due to progressive disease after being treated with continuous androgen deprivation therapy and receiving docetaxel and enzalutamide followed by abiraterone acetate. He had transient improvement in his metastatic CRPC in response to these therapies; but overall, his course was characterized by disease progression with rising PSA levels. On admission, the Eastern Cooperative Oncology Group performance status (PS) was 2 and vital signs were within the normal range. Lower back pain was present.

Laboratory data showed a white blood cell count of 4,900 /mm^3, platelet count of 117,000 /mm^3, hemoglobin of 10.0 g/l, international normalized ratio for prothrombin time of 1.12, fibrinogen level of 261 mg/dl, fibrin degradation products of 16 μg/ml, d-dimer level of 10.2 μg/ml, thrombin-antithrombin complex of 16.5 ng/ml, C-reactive protein level of 3.32 mg/dl, pyridinoline crosslinked carboxyterminal telopeptide of type I collagen (1CTP) of 34.3 ng/ml, creatinine level of 1.17 mg/dl, calcium level of 8.7 mg/dl, albumin level of 3.5 mg/dl, total bilirubin level of 0.46 mg/dl, aspartate aminotransferase level of 81 U/l, alanine aminotransferase level of 20 U/l, alkaline phosphatase level of 944 U/l, and lactate dehydrogenase level of 655 U/l. Estimated glomerular filtration rate (eGFR) was 34 ml/minute/1.73 m^2. These laboratory data suggested that the patient did not have disseminated intravascular coagulation (DIC), but had renal dysfunction. Whole body Tc-99m-methylene diphosphonate bone scan demonstrated multiple foci of increased activities in the both humeruses, scapulas, ribs, vertebrae, femurs, and pelvis (Figure 1). Based on the laboratory data and bone scintigraphy findings, Ra-223 (Xofigo, Bayer Health Care Pharmaceuticals Inc., Whippany, NJ, USA) was indicated for the treatment of metastatic CRPC.

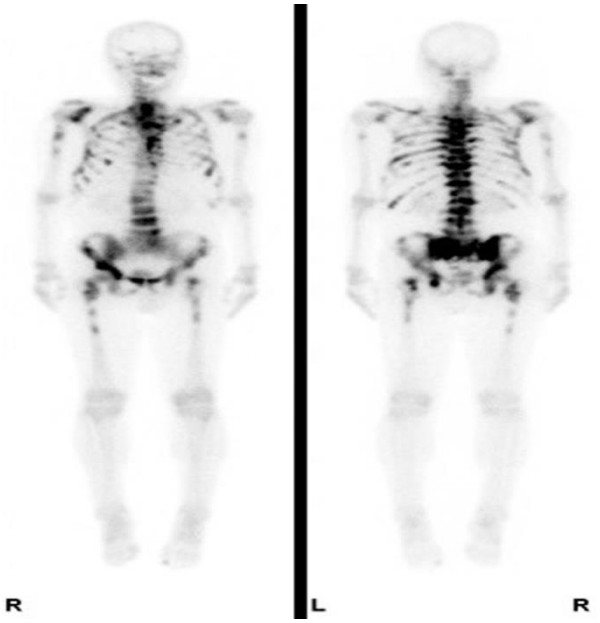

Figure 1. Anterior (left) and posterior (right) whole-body bone scintigrams obtained after injection of Tc-99m-methylene diphosphonate demonstrated multiple foci of increased activities in both humeruses, scapulas, ribs, vertebrae, femurs, and pelvis prior to administration of Ra-223

As the patient had met the requirements of administering Ra-223, 55 kBq/kg (114 MBq/body) solution of Ra-223 was injected intravenously with no acute adverse events. There was no improvement of

subjective symptoms of back pain and leg pain during the first week after Ra-223 injection. One week later, laboratory data showed a white blood cell count of 2,700 /mm^3 (absolute neutrophil count: 1,848 /mm^3), platelet count of 30,000 /mm^3, hemoglobin of 8.0 g/l, international normalized ratio for prothrombin time of 1.16, fibrinogen level of 281.8 mg/dl, d-dimer level of 2.7 μg/ml, and C-reactive protein level of 8.88 mg/dl. Based on the laboratory data, hematologic toxicity of Ra-223 was suspected. At 2 weeks after Ra-223 administration, the pancytopenia was further exacerbated with a white blood cell count of 2,200 /mm^3, platelet count of 16,000 /mm^3, hemoglobin of 6.7 g/l. Chest CT scan revealed diffuse ground glass opacities in the left lower lobe and bilateral pleural effusions (Figure 2), which was suggestive of pneumonia secondary to hematologic toxicities. The hematologic toxicities were treated with blood transfusion; however, the patient died from progressively exacerbated pancytopenia 4 weeks after administration of Ra-223.

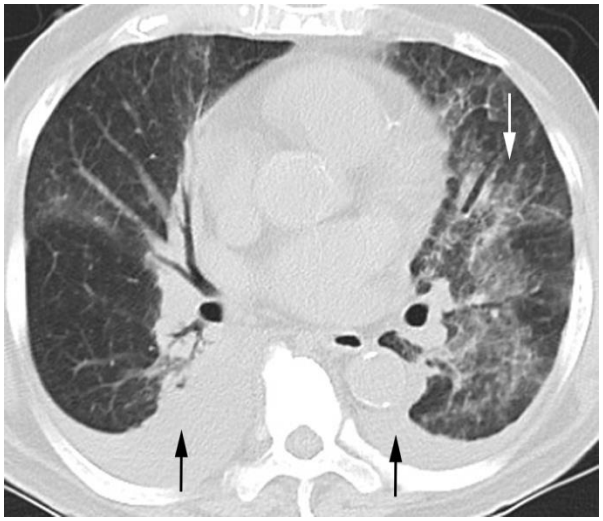

Figure 2. Chest computed tomography (CT) scan revealed diffuse ground glass opacities (white arrow) in the left lower lobe and bilateral pleural effusions (black arrows).

Discussion

In the phase 3, randomized-controlled ALSYMPCA trial, only one (< 1%) fatal hematologic adverse event was considered to possibly related to Ra-223; thrombocytopenia in a patient who died from pneumonia with hypoxemia, with no evidence of bleeding (2). The highly targeted nature of Ra-223, with alpha particles of short range (< 100 μm) and short half-life (11.4 days) minimizes myelosuppression, and has limited effects on normal tissue. The overall incidence of adverse events was consistently lower in the Ra-223 group than in the placebo group for adverse events of all grades, grade 3 or 4 adverse events, and serious adverse events (2). As far as we know, this is the first fatal case of hematologic complications after Ra-223 was approved by the United States Food and Drug Administration (US FDA).

In this case, absolute neutrophil count, platelet count, and hemoglobin level were all confirmed to fulfill the selection criteria for treatment of metastatic CRPC with Ra-223: absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, and hemoglobin $\geq$ 10 g/dl. One possible explanation for the observed hematological toxicity at this dose level (55 kBq/kg or 114 MBq/body) was reduced kidney function (eGFR of 34 ml/minute/1.73 m^2).

After intravenous administration, Ra-223 is rapidly eliminated from plasma into tissues, mainly bones and small bowel, with minimal biliary and renal excretion (5). Although compared with the beta-emitters, the radiation emitted by Ra-223 is more limited, with a much shorter track length of less than 0.1 mm in tissue, compared with 0.6 mm for samarium-153 and 2.4 mm for strontium-89, offering the advantage of less myelosuppression. But, this patient had been treated for systemic edema and constipation during and after the treatment with abiraterone acetate and prednisone, and also his kidney function was significantly impaired. Under such conditions, systemic edema, constipation, and decline of renal function, clearance of Ra-223 should be impaired and ultimately large amounts of bone marrow will be exposed to high doses of radiation.

Although a single case report cannot be generalized to others without further scientific verification, particular caution should be paid to a patient with systemic edema, constipation, and decline of renal function when administering Ra-223.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

None.

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