Review

Hematologic Toxicity From Radium-223 Therapy for Bone Metastases in Castration-Resistant Prostate Cancer: Risk Factors and Practical Considerations

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Abstract

Radium-223 is a radiopharmaceutical localizing to bone and is approved for treatment of bone metastases in prostate cancer. Safety and efficacy data regarding hematologic events from radium-223 therapy are discussed.

Radium-223 dichloride is an α-emitting radiopharmaceutical that localizes to bone matrix and is approved for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) and symptomatic bone metastases. The cumulative impact of Ra-223 and other therapeutic agents for metastatic CRPC on myelosuppression in bone marrow is unknown. The phase 3 randomized, double-blind, placebo-controlled ALSYMPCA trial of Ra-223 in patients with CRPC and symptomatic bone metastases demonstrated a significant improvement in overall survival. Of the 571 patients subsequently followed for 3 years, few in either the Ra-223 or placebo arm experienced hematologic adverse events. Little evidence shows secondary malignancies associated with Ra-223 treatment; only 2 cases of secondary leukemia after Ra-223 treatment were found in the literature. The goals of this review were to summarize safety and efficacy results from clinical trials and institutional safety data pertaining to hematologic adverse events occurring with Ra-223, and to discuss practical management issues.

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Introduction

Prostate cancer is the most common cancer in men in the United States.[1,2] Metastatic castration-resistant prostate cancer (CRPC) represents end-stage disease affecting approximately 40,000 men in the United States.[3] The 5-year overall survival (OS) for men with metastatic CRPC (mCRPC) is 29%.[4] Most (~ 90%) patients with mCRPC develop bone metastases,[5] a significant cause of morbidity and mortality.[6]

Since 2010, the armamentarium of drugs to treat CRPC has expanded. Androgen pathway inhibitors abiraterone and enzalutamide, chemotherapy agent cabazitaxel, and sipuleucel-T immunotherapy have improved survival and are often provided sequentially. Radium-223 dichloride (Ra-223) is a bone-seeking targeted alpha (α)-emitting radiopharmaceutical also recently approved for the treatment of symptomatic bone metastases. Whereas the β-emitting radiopharmaceuticals strontium-89 and samarium-153 are used for pain palliation of bone metastases, treatment with Ra-223 provides a survival advantage in patients with mCRPC.[7]

Ra-223 has advantages over external beam radiotherapy (EBRT), analgesics, and osteoclast inhibitors for mitigating skeleton-related events. EBRT is suited only for well-defined bone metastases, and extended field radiation is often accompanied by significant adverse events (AEs). Osteoclast inhibitors do not affect survival but instead slow or reverse progression of bone metastases and improve bone mineral density.[8,9]

Myelosuppression is a common AE associated with several treatments for mCRPC,[8] but the cumulative impact of sequential

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therapies on bone marrow is unknown. A confounding factor is that myelosuppression often occurs in mCRPC related to infiltrative bone disease.[10] Questions remain regarding appropriate sequencing of available agents to maximize therapeutic benefit while preserving bone marrow reserve for future treatment. Data are needed on optimally integrating Ra-223 therapy into existing treatment options for men with mCRPC.

The goals of this review were to summarize safety and efficacy results from clinical trials and institutional safety data pertaining to hematologic AEs occurring with Ra-223, and to discuss practical management issues.

Mechanism of Action of Ra-223

Ra-223 is an α-emitting radionuclide that localizes to bone matrix by binding to bone mineral hydroxyapatite.[11] Ra-223 decay events result in high linear energy transfer delivery to the surrounding environment, leading to a high frequency of double-stranded DNA breaks in adjacent tumor cells and subsequently to cancer cell death. The α-particle range of Ra-223 is < 100 μm, thereby theoretically maximizing dose to cortical bone and metastatic cells while minimizing dose to the marrow and other normal tissues. Ra-223 has a rapid decay cascade, which limits the diffusion of radioactive daughter nuclides.[7,11] These properties of Ra-223 α-particles are advantageous because the frequency of lethal double-stranded DNA breaks to tumor cells is higher, with less hematologic toxicity, compared to β particles of samarium-153 and strontium-89.[12]

Efficacy and Nonhematologic Toxicity of Ra-223

The phase 3 randomized, double-blind, placebo-controlled ALSYMPCA clinical trial with Ra-223 (NCT00699751; n = 921) in patients with CRPC and symptomatic bone metastases demonstrated a 30% reduction in the risk for death versus standard of care[7,13] and a significant improvement in OS (median, +3.6 months), regardless of previous docetaxel use.[7,13,14] The time to first skeleton-related event was significantly longer with Ra-223 compared to the standard of care (median, 15.6 vs. 9.8 months, respectively; $P = .00037$),[7,13] and the Eastern Cooperative Oncology Group performance scores improved in the Ra-223 group.[11]

Recent analysis of European Quality of Life-5 Dimensions (EQ-5D) questionnaire and Functional Assessment of Cancer Therapy-Prostate (FACT-P) data from the ALSYMPCA trial demonstrated a slower decline of quality of life over time and a meaningful improvement in EQ-5D utility and FACT-P total score in the Ra-223 group versus the standard-of-care group.[15,16]

The efficacy of Ra-223 was evaluated in expanded-access programs.[17,18] In the first expanded-access program, patients (n = 184) with fewer previous treatments completed more cycles of Ra-223 than did patients who received more previous treatments.[17] In the second expanded-access program (n = 696), OS was higher in patients who received concomitant denosumab or abiraterone, and longer OS was observed in patients with good Eastern Cooperative Oncology Group performance scores, no pain, and low alkaline phosphatase (ALP) levels.[18]

Ra-223 was well tolerated in ALSYMPCA. Nonhematologic grade 3/4 AEs (incidence ≥ 5%) were not significantly different between the Ra-223 and placebo groups and included fatigue (5% vs. 6%), bone pain (21% vs. 26%), and spinal cord compression (3% vs. 6%), respectively.[7] In a post hoc analysis, treatment discontinuation due to AEs was similar in patients receiving Ra-223 compared to patients receiving placebo, indicating a positive Ra-223 treatment effect and safety profile (Table 1).[19] Overall, 65% (391/600) of patients in the Ra-223 group and 48% (144/301) of patients in the placebo group received all of the recommended 6 injections. The most common AE leading to treatment discontinuation was disease progression (Table 1).[19]

Hematologic Safety of Ra-223

Overall rates of hematologic AEs in ALSYMPCA were low in the Ra-223 group and were similar to placebo (Table 2).[20,21] There were no significant differences between Ra-223 and placebo for all grades of anemia (31% vs. 31%, respectively) or grade 3/4 anemia (13% vs. 13%, respectively). Grade 3/4 neutropenia rates were not significantly different between the Ra-223 and placebo groups (2% vs. 1%, respectively), although more neutropenia was observed with Ra-223 compared to placebo for all grades (5% vs. 1%, respectively; $P = .005$). Grade 3 febrile neutropenia occurred in 1 (< 1%) of 600 patients who received Ra-223 and in 1 (< 1%) of 301 patients who received placebo.[19] The rates of thrombocytopenia were significantly higher in the Ra-223 group than in the placebo group for all grades (12% vs. 6%, respectively; $P = .002$) and for grade 3/4 (6% vs. 3%, respectively). One patient in the Ra-223 group had grade 5 bone marrow failure related to the study drug.[20]

Of the 901 patients in the ALSYMPCA safety population, 571 entered the 3-year follow-up period, wherein the incidence of hematologic AEs was low (Table 2).[20,21] There were no reports of acute myelogenous leukemia, myelodysplastic syndrome, or new primary bone cancers at the end of this period (Table 2).[20,21]

Table 1 Adverse Events Leading to Study Discontinuation in ≥ 1% Patients Receiving Radium-223 in ALSYMPCA Trial

Adverse Event	Radium-223 (N = 209)[a]	Placebo (N = 157)	P[b]
Disease progression	16 (8)	10 (6)	.69
Anemia	12 (6)	1 (1)	.01
General health deterioration	8 (4)	1 (1)	.08
Thrombocytopenia	7 (3)	3 (2)	.15
Spinal cord compression	5 (2)	3 (2)	1
Fatigue	4 (2)	5 (3)	.51
Neutropenia	3 (1)	1 (1)	.64
Bone pain	2 (1)	7 (4)	.42
Cerebral hemorrhage	2 (1)	1 (1)	1
Lymphadenopathy	2 (1)	—	.51
Metastasis to CNS	2 (1)	1 (1)	1
Osteonecrosis	2 (1)	—	.51
Sepsis	2 (1)	—	.51

Data are presented as n (%).
Abbreviation: CNS = central nervous system.
[a]Calculated as percentage of total adverse events as reasons for discontinuation. Dash indicates no reported cases of adverse event.
[b]*P* values calculated from original data in reference 19 poster using Fisher's exact test (2 × 2 contingency table).
Data adapted from Logue J, Wedel S, Chodacki A, et al. Ann Oncol *2014; 25:iv264-5.*[19]