Editorial

Radium-223 and concomitant therapies: prospects and prudence

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Most patients with relapsed prostate cancer develop metastatic disease and eventually become castration-resistant. Skeletal metastasis is common in castrate resistant prostate cancer and is an independent poor prognostic factor (1). Furthermore, skeletal related events (SRE) such as spinal cord compression, pathologic fractures and requirement for external beam radiation for pain palliation continue to represent a significant cause of morbidity for patients with bone metastasis (2). Over the last decade, significant strides have been made in the development of therapies for patients with castrate resistant metastatic prostate cancer (CRPC). Abiraterone (Zytiga®) (3), and Enzalutamide (Xtandi®) (4) were approved based on data supporting improved overall survival compared to placebo and in addition, both agents decreased time to SRE and increased rates of pain palliation in the case of Abiraterone. More recently, Radium-223 (Xofigo®) became the first approved radiopharmaceutical which decreased SRE's, palliated pain, and showed improved overall survival in symptomatic or minimally symptomatic patients with CRPC and bone metastasis only (5). As such, both the American Society of Clinical Oncologists and the American Urologic Association have recommended incorporation of Radium-223 into the treatment algorithm (6,7). Ongoing debate has focused on the initiation of Radium-223 earlier in the disease course and the question of safety and efficacy of combining Radium-223 with other AR-directed therapies (8).

In a recently published article, Saad *et al*. (9) conducted a single-arm, phase 3b, international multicenter clinical trial investigating the safety and efficacy of radium-223 and concomitant therapies in 696 patients with CRPC. The trial involved a majority of Caucasian men aged 65 years and older with bone-predominant disease with at least two or more skeletal metastases. Although, men with nodal disease were permitted, patients with visceral metastases were excluded from the study. Patients could receive concomitant administration of abiraterone, enzalutamide, or denosumab. The primary endpoints for the study were safety and overall survival. After a median follow-up of 7.5 months, the authors reported improved overall survival in patients who received concomitant radium-223 and either abiraterone, enzalutamide, abiraterone and enzalutamide or denosumab. The same benefit did not extend to patients undergoing treatment with radium-223 and bisphosphonates. Combination treatment was reported to be well-tolerated. Discontinuation of radium-223 due to adverse effects occurred in 21% patients. Grade 1–2 adverse effects occurred in 32% of patients and 37% of patients experienced any grade 3–4 toxicity. The most common adverse effect was grade 3 anemia (12%) and combined grade 3–4 cytopenia (anemia, thrombocytopenia, leucopenia and neutropenia) occurred in 20% of patients.

This study raises the potential of radium-233 and AR-directed therapy to synergize and modulate the bone-tumor microenvironment. The cellular and molecular mechanisms of prostate cancer dissemination and survival in the bone microenvironment have been well-described. For instance, prostate cancer cells have been shown to have

preferential affinity for the osteoclastic niche via annexin II-mediated binding to osteoclasts (10). Additionally, tumor cells secrete bioactive substances such as insulin-like growth factor (IGF), fibroblast growth factor (FGF) and bone morphogenetic factor which have been shown to promote osteoblast differentiation and activity (11). This pathologic bone remodeling process is further promoted by RANKL produced by osteoblasts (12). Other stromal-derived cells such as tumor associated macrophages and myeloid derived suppressor cells have been shown to promote tumor progression in the bone microenvironment (13). Upon dissemination, prostate cancer tumor cells have also been shown to compete with hematopoietic stem cells via upregulation of CXCR4 by competing with CXCL12 binding partners on bone marrow endothelial cells, stromal cells and osteoblasts (14). Abiraterone has been shown to induce osteoblast differentiation and bone matrix deposition in addition to inhibiting osteoclast differentiation and activity (15). Additionally, in a mouse model of both osteoblastic and osteoclastic metastatic prostate cancer, radium-223 was found to localize to the surrounding bone around the tumor without localizing within the tumor itself (16). Radium-223 was also reported to localize to regions of active bone remodeling. Based on these observations, one could posit that the combination of decreased pathologic bone turnover and tumor irradiation by radium-223 could be responsible for the improved outcomes described in the study by Saad *et al*. (9). Another hypothesis involves the role of high Linear Energy Transfer (LET) radionuclides, such as radium-223, to induce bystander cytotoxicity (17). Bystander cytotoxicity is a phenomenon by which cells that have not been directly exposed to radiation are damaged by being in the proximity of cells previously exposed to and damaged by radiation. This study by Saad *et al*. (9) raises exciting possibilities for mechanism-derived combinatorial therapy for CRPC.

Enthusiasm for this report has to be tempered in the context that only 58% of patients received all six injections of radium-223. Although considered to be well-tolerated, the rate of grade 3/4 cytopenias reported in this trial is reason for careful consideration in clinical practice. In at least one report, delayed or persistent hematologic toxicity was noted in prostate cancer patients with high tumor burden receiving radium-223 therapy (18). Persistent or transfusion-dependent cytopenias could render future treatment with cytotoxic chemotherapy more challenging if patients progress on concomitant-radium therapy. Due to the relatively short median follow-up period of this trial, i.e., 7.5 months, it has yet to be determined whether or not there will be any delayed or persistent marrow toxicity with these combinations. There are published computational methods that can be used to model the degree of marrow toxicity from radium-223 (19). Ultimately, the radium-223 dose and number of infusions required for combinatorial therapy might be less than the currently approved dose for monotherapy. Also unknown is how this combination might lead to emergence of highly treatment-resistant prostate cancer due to alteration of the tumor biology. We cannot ensure that in doing these treatments, we will not be incurring mutations of resistance, such as AR-V7 (20), that could lead to earlier treatment failure.

To counter this argument, is the possibility to offer a combinatorial approach with radium-223 that could delay or actively treat the progression to highly resistant disease by providing non-AR-dependent cytotoxicity in combination with AR-directed killing. Ultimately, these experiments will be need to be conducted in preclinical animal models with concurrent assessment of clinical correlates. As new, highly effective therapies for CRPC have emerged, the issue of when and what treatments to sequence or combine has been a challenging issue for clinicians. If a patient with docetaxel-resistant metastatic CRPC to bone progresses on concomitant radium-223 therapy used in the absence of symptoms, the options left for treatment of multifocal bone pain later in the course of the disease becomes dramatically limited. Since definitive data regarding the safety and efficacy of radium-223 retreatment in post-docetaxel patients is forthcoming, these considerations need to anticipated.

Data regarding the safety of concomitant abiraterone, enzalutamide or denosumab with radium-223 from this study is reassuring and timely. Other issues related to the "non-blinded" nature of the study, absence of SRE as an endpoint, optimal dosing of radium for combined therapy and length of follow up are likely to be addressed in upcoming clinical trials. Pending more conclusive results, we cannot advocate at this time for the general use of combined radium-223 therapy in all men with CRPC irrespective of prior therapy, especially pre-chemotherapy. For now, this safety data should be used to guide conversations with highly selected patients who might benefit from the addition of radium-223 to ongoing abiraterone or enzalutamide therapy. Although promising, the additional overall survival benefit (16 months) reported in this trial *vs*. 14.9 months (5) will need to be confirmed in randomized blinded phase 3 studies.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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