



Radium-223 dichloride for metastatic prostate cancer: long-term safety profile and future opportunities

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Prostate cancer is the most common new cancer diagnosis and the second leading cause of cancer death in men in the United States. Worldwide, it is the second most common cancer in men (1). As a result of screening, the majority of new cases are diagnosed when the disease is localized and can be cured. For patients who develop metastatic disease, androgen deprivation therapy (ADT) has been the first line of treatment. Unfortunately, the disease eventually becomes castration-resistant [metastatic castration-resistant prostate cancer (mCRPC)], causing significant morbidity and mortality. There had been little progress in systemic therapy for mCRPC until 2004 when two randomized studies demonstrated that docetaxel improved the overall survival of these patients (2,3). In the last decade, five more new agents have been approved by the FDA for the treatment of mCRPC, the most recent one being radium-223 (^{223}Ra) dichloride in 2013. In the ALSYMPCA study, patients with mCRPC were randomized to ^{223}Ra or placebo (4). There was a significant improvement in median survival in patients receiving ^{223}Ra for mCRPC as compared to placebo (14.9 *vs.* 11.3 months).

^{223}Ra is an α -emitter that causes double-strand DNA break of cells. It forms complexes with bone mineral hydroxyapatite in areas of active bone remodeling. With a range of penetration of $<100\ \mu\text{m}$, ^{223}Ra can achieve localized killing of cancer cells while minimizing side effects to the nearby bone marrow. In the ALSYMPCA study, ^{223}Ra was well-tolerated with low incidence of serious acute toxicities. In a recent report, the investigators of the ALYSYMPCA

study updated the long-term safety data of the drug (5). Patients entered long-term safety follow-up starting 12 weeks after the last ^{223}Ra administration, and were followed up to 3 years from the first injection. Of the 901 patients in the study, 572 entered the 3-year follow-up, including 405 patients in the ^{223}Ra group (68%), and 167 patients in the placebo group (55%). The median follow-up time from the first injection up to 3 years was 13 months for ^{223}Ra patients and 9 months for placebo patients. ^{223}Ra was well-tolerated with low incidence of acute toxicities. Grade 3 and 4 myelosuppression included 13% anemia, 2% neutropenia and 1% thrombocytopenia. Among the non-hematologic toxicities, there was more diarrhea in the ^{223}Ra group (26%) than the placebo group (15%). The most frequently reported treatment emergent adverse events (TEAE) from the time of first ^{223}Ra administration up to 12 weeks after the last injection were disease progression leading to death, accounting for 9% of the ^{223}Ra group and 12% of the placebo group, respectively. Secondary malignancies occurred in five patients in the ^{223}Ra group and two patients in the placebo group.

For patients who entered long-term follow-up, the majority did not complete the 3-year follow-up. The main cause of discontinuation was death. Overall incidences of myelosuppression during long-term follow-up were 5% for the ^{223}Ra group and 3% for the placebo group. Non-hematologic toxicities were minimal. There were no reports of acute myelogenous leukemia (AML) or myelodysplastic syndrome. In the ^{223}Ra group, one patient was diagnosed

to have aplastic anemia at 3 months after completion of the treatment. There were two other cases of secondary malignancies that were considered unrelated to ^{223}Ra treatment. In the placebo group, three cases of secondary malignancies were reported. The cumulative incidence rates for hematologic and non-hematologic adverse events and secondary malignancies were low, as illustrated in supplemental Table 5 of the article. The deaths of two ^{223}Ra patients, one from pneumonia and one from multi-organ failure, were thought to be related to the treatment. The authors acknowledged that a 3-year follow-up time was relatively short to assess treatment induced secondary malignancy.

The 3-year safety data for ^{223}Ra were reassuring. The late hematologic and non-hematologic side effects were low and acceptable. However, the short median follow-up time was a major limitation of the study. The median follow-up time was 13 months for the ^{223}Ra patients and 9 months for the placebo patients. The latent time for the development of treatment-associated secondary malignancy (TASM) would take several years, and the short follow-up time for these patients might not be sufficient to observe the development of these events. In patients who received ^{32}P for polycythemia vera and essential thrombocythemia, the median time to the development of leukemia was 8.5 years (6). In patients who received external beam irradiation and/or chemotherapy for Hodgkin lymphoma, TASM were seen after more than 5 years of treatment completion (7). Increased incidences of AML have been associated with the use of ^{224}Ra in the treatment of ankylosing spondylitis. In a prospective epidemiologic study by Wick *et al.*, 1,471 patients were treated with a mean dose of 0.17 MBq/kg of ^{224}Ra (8). After a mean follow-up of 26 years, 19 cases of leukemia were observed, as compared to 7.5 cases expected. There was also a case report of acute promyelocytic leukemia (APML) in a patient with mCRPC 18 months after the last dose of ^{223}Ra (9). However, the authors did not feel that ^{223}Ra was the cause of the leukemia because of the short latency time and the pathology of APML instead of AML.

Another limitation of the study was the small number of patients followed to 3 years. Only 48 (12%) of the ^{223}Ra patients and 12 (7%) of the placebo patients completed the 3-year follow-up as a result of cancer death. The small number of patients followed to 3 years would reduce the probability of detecting a small to modest increased risk of TASM. Patients with mCRPC have a poor prognosis. In the ALYMPCA study, the median survival of patients receiving

^{223}Ra was 14.9 months, meaning that most of them would not live long enough to experience TASM. Thus, the data reported by Parker *et al.* would not fully evaluate the risk of TASM of ^{223}Ra .

The 3.6 months improvement in median survival from ^{223}Ra for patients with mCRPC is quite modest. The future opportunity for this radiopharmaceutical to play a major role in metastatic prostate cancer depends on whether it can achieve a much longer survival of these patients when it is used earlier in the natural history of the disease. Conventional management approach for metastatic prostate cancer is to use ADT as first line therapy and add cytotoxic systemic agents sequentially after the disease becomes castration-resistant. Recently, several randomized studies challenge such treatment paradigm. In these trials, instead of ADT alone as the initial therapy, systemic therapy with a different mechanism of action than ADT was added to ADT for patients with newly diagnosed metastatic prostate cancer before the disease becomes castration-resistant. In the CHARRTED trial, patients who received docetaxel + ADT had a median survival of 57.6 months, as compared to 44 months with ADT alone (10). There was an improvement in median survival of 13.6 months. The survival benefit was seen mainly in patients with high volume disease, defined as ≥ 4 metastatic bone lesions (median survival of 49.2 *vs.* 32.2 months). In the STAMPEDE trial, patients with advanced prostate cancer had an improvement in median survival of 10 months with docetaxel + standard of care (i.e., ADT), as compared to the standard of care group (median survival: 81 *vs.* 71 months) (11). In the LATITUDE trial comparing abiraterone + ADT to ADT alone for castration-sensitive metastatic prostate cancer, the median survival had not been reached in the combination group, as compared to 34.7 months in the ADT group (12). Similar findings were reported by James *et al.*, comparing abiraterone + ADT to ADT alone as first-line therapy. They showed a significant decrease in cancer death (hazard ratio: 0.63) at a median follow-up of 40 months (13). The findings of these four randomized trials suggest that early use of systemic agents with different mechanism of action than ADT can achieve significantly better survival than ADT alone in patients with castration-sensitive metastatic prostate cancer.

Based on the results of the aforementioned randomized trials, a very important question to ask is whether the use of ^{223}Ra in patients with castration-sensitive metastatic prostate cancer can achieve greater improvement in survival than the 3 to 4 months seen in patients with mCRPC. A randomized trial would be necessary to provide the answer

to this question. If the early use of ^{223}Ra in combination with ADT for castration-sensitive metastatic prostate cancer can achieve a median survival in the range of 50–80 months, these patients may survive long enough to encounter TASM as a late side effect. In such case, better understanding of the risk of TASM would be more relevant. An ongoing trial by the Hoosier Cancer Research Network GU13-170 (NCT02582749) compares ADT + ^{223}Ra to ^{223}Ra alone for patients with newly diagnosed metastatic prostate cancer, with a primary endpoint of radiographic progression-free survival.

In summary, the 3-year safety data of ^{223}Ra show low probability of serious side effects. However, the risk of TASM cannot be fully assessed due to the short survival time of patients with mCRPC. Vigorous post-market monitoring of the development of TASM as a late toxicity is necessary to identify such a trend. This is especially important if the survival of patients with metastatic prostate cancer improves significantly with improvement in systemic therapy.

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