Review Article

Radioisotopes in management of metastatic prostate cancer

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ABSTRACT

Introduction: Metastatic prostate cancer continues to be a leading cause of morbidity and mortality in men with prostate cancer. Over the last decade, the treatment landscape for patients with castrate-resistant disease has drastically changed, with several novel agents demonstrating an improvement in overall survival in large, multi-institutional randomized trials. Traditional treatment with radioisotopes has largely been in the palliative setting. However, the first in class radiopharmaceutical radium-223 has emerged as the only bone-directed treatment option demonstrating an improvement in overall survival.

Methods: Medline publications from 1990 to 2016 were searched and reviewed to assess the use of currently approved radioisotopes in the management of prostate cancer including emerging data regarding integration with novel systemic therapies. New positron emission tomography-based radiotracers for advanced molecular imaging of prostate cancer were also queried.

Results: Radioisotopes play a crucial role in the diagnosis and treatment of prostate cancer in the definitive and metastatic setting. Molecular imaging of prostate cancer and theranostics are currently being investigated in the clinical arena.

Conclusions: The use of modern radioisotopes in selected patients with mCRPC is associated with improvements in overall survival, pain control, and quality of life.

Key words: Alpha particle, alpharadin, bone metastases, bone-targeting, calcium mimetic, metastatic castrate, resistant prostate cancer, radionuclide, radiopharmaceutical, radium-223

INTRODUCTION

Metastatic prostate cancer is a leading cause of morbidity and mortality in men, with approximately 30,000 deaths in 2015.[1] Despite advances in definitive therapy, the development of metastatic disease remains common. Currently, consensus guidelines regarding treatment for metastatic castrate-resistant prostate cancer (mCRPC) remains an area of controversy.[2] Several novel agents have now demonstrated an improvement in overall survival although the ideal sequencing and integration of these therapies with established treatments are still under investigation. Among these, novel agents include the use the radioisotope radium-223 (Ra-223), which is a first-in-class radioisotope demonstrating an improvement in overall survival.

METHODS

Medline publications from 1990 to 2016 were searched and reviewed to assess the use of currently approved radioisotopes in the management of prostate cancer. Medline was searched using one or several combinations of the following items: "Radioisotope," "Radiopharmaceutical," "Radium-223,"

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"Strontium-89," "Samarium-153," "Rhenium," "Indium-111," "PSMA," "Ga-68," "F-18," "Tc-99m," "Lu-177," and "I-131." Only prospective and randomized trials were included when reporting clinical data.

BONE METASTASES IN PROSTATE CANCER

Metastatic prostate cancer overwhelmingly involves osseous structures in the body. Metastatic deposits are a leading cause of morbidity and mortality due to the significant impact on one's functionality and quality of life (QOL). Mechanisms determining the exact involvement of osseous structures are currently unknown; however, it is thought it may involve the complex interplay in the bone microenvironment.[3] A continuous balance between osteoclast and osteoblast activity regulates bone homeostasis. With increased osteoblast activity, calcium utilization is increased, suggesting targeted treatment with calcium-mimetics may be an effective treatment strategy.

RADIOISOTOPES IN PROSTATE CANCER

Radioisotopes directed to the bone remodeling system have previously been utilized in diagnostic imaging of osseous metastases. The most used radioisotope in this regard has been technetium-99 methylene (Tc-99m) diphosphonate bone scintigraphy. Newer modalities such as sodium fluoride positron emission tomography (PET) and 18-fluorodeoxyglucose (F-18) PET have also demonstrated promise.[4] A natural extension of this application has been for therapeutic purposes, particularly in prostate cancer due to the predilection of bone-only metastases. A number of randomized trials have demonstrated the efficacy of radioisotopes although their application has been mostly in the palliative setting. Agents used in a therapeutic setting against metastatic prostate cancer include strontium-89, samarium-153, rhenium-186, and rhenium-188, and most recently, Ra-223. The physical characteristics of these agents are shown in Table 1.

STRONTIUM-89

Strontium-89 received Food and Drug Administration (FDA) approval in 1993 for use in the treatment of painful bone metastases.[5] Strontium-89 is a calcium-mimetic that decays as pure beta-emitter. When compared to normal bone, there is 10-fold uptake increase into bone containing metastases.[6] There have been several randomized trials evaluating the efficacy of strontium-89 in the palliative setting. In one systematic review, complete pain response was reported from 8% to 77% with a partial pain response in 44% of patients.[7] The most common toxicities associated with administration include leukopenia and thrombocytopenia.

Table 1: Characteristics of Approved Radioisotopes in mCRPC

Radionuclide	Half-life (days)	Decay particle	Tissue penetration (mm)
Radium-223	11.4	Alpha	<0.1
Strontium-89	50.5	beta	5.5
Samarium-153	1.9	beta, gamma	2.5
Rhenium-186	3.8	beta, gamma	4.5
Rhenium-188	7	beta, gamma	11.0

SAMARIUM-153

Samarium-153 is another beta-emitter with a minor component of γ emission. Unlike other therapeutic radionuclides, it is not a calcium-mimetic. Instead, it is complexed with ethylenediamine tetramethylene phosphonate (EDTMP), which binds to bone in association with hydroxyapatite. It has a five times greater affinity to tumor than normal bone.[8] Similar to strontium, there have been multiple randomized phase III trials demonstrating an improvement in bone pain and reduced analgesic use with its use. Overall response rates range from 60% to 80%, depending on study-defined criteria.[9-11]

RHENIUM

Other radionuclides utilized in the palliative setting include rhenium hydroxyethylidene diphosphonate (HEDP) and its isotopes rhenium-186 and rhenium-188. These isotopes are agents that have both significant β and γ emission, allowing for usage in for therapeutic and diagnostic purposes. Studies utilizing rhenium appear to have response rates ranging from ~40% to 80%.[12] Both agents appear to demonstrate some evidence for pain relief, with no difference between the two in terms of pain palliation, analgesic use, or bone marrow toxicity.[13]

RADIUM-223

Unlike the other radioisotopes used in this disease, Ra-223 relies on alpha-decay to exert its therapeutic properties. Historically, primary outcomes in studies utilizing beta-emitters have included pain response, decrease in analgesic consumption, and QOL as noted above. However, due to its unique properties, clinical efficacy with Ra-223 has been demonstrated with improvements in overall survival in a prospective and randomized fashion.

RADIUM-223 CLINICAL DATA

Results from the phase III international ALpharadin in SYMptomatic Prostate CAncer (ALSYMPCA) trial prompted FDA approval of Ra-223 in men with mCRPC. This trial randomly assigned 928 men with painful bone metastases from mCRPC to receive 50 kBq/kg of Ra-223 monthly for 6 doses versus placebo in conjunction with standard care.[14]

In this landmark trial, there was significantly improved overall survival (median 14.0 vs. 11.2 months; hazard ratio, 0.70 $P = 0.002$). Secondary endpoints including time to the first symptomatic skeletal-related event (SRE), time to an increase in the total alkaline phosphatase level (ALP), and the time to an increase in the prostate-specific antigen (PSA) level were all demonstrated to be superior in the radium arm. In the updated report on symptomatic skeletal events, SREs occurred in 202 (33%) of 614 patients in the Ra-223 group and 116 (38%) of 307 patients in the placebo group.[15] The risks of external beam radiation therapy for bone pain and spinal cord compression were reduced with the use of Ra-223 compared with placebo. In addition, improvement in overall survival was accompanied by significant QOL benefits including a higher percentage of patients with meaningful QOL improvement and a slower decline in QOL over time.[16]

In recent follow-up studies, biomarker analysis of serum ALP was investigated in Phase II Japanese trial based on *post hoc* analysis from the ALSYMPCA trial which delineated a reduction in total ALP from baseline at 12 weeks, correlating with an improvement in overall survival. The mean percentage of decrease of total ALP from baseline at 12 weeks was a 19.3%, confirming the significant improvement of metastatic osseous disease.[17] However, in a retrospective analysis, a number of patients with an increase in PSA and decrease in ALP were demonstrated to have no clinical benefit.[18]

TOXICITY

In comparison to other radioisotopes, Ra-223 is associated with an overall low incidence of grade 3 or 4 myelosuppression. Although excreted by the gastrointestinal tract, there was a low incidence of grade 3 or 4 gastrointestinal adverse events (AEs) (diarrhea, 2% vs. 2% placebo; vomiting, 2% vs. 2%; and constipation, 1% vs. 1%). In the 3-year follow-up for AEs, 27/405 (7%) of Ra-223 patients and 8/167 (5%) of placebo patients had 42 treatment-related AEs.[19] Myelosuppression incidence was ≤3%. No patients developed acute myeloid leukemia, myelodysplastic syndrome, or primary bone cancer.

In the prespecified subgroup analysis of patients, investigators found that patients who have previously received docetaxel had an increased risk of hematological toxicity compared with those with no previous docetaxel use.[20] However, only grade 3–4 thrombocytopenia appeared to be increased in this subgroup. The investigators did not report any differences in nonhematological AEs between the subgroups.

Furthermore, in a recent international study investigating retreatment with Ra-223, investigators found that retreatment was well tolerated with minimal morbidity while mitigating bone disease progression.[21]

SEQUENCING WITH OTHER SYSTEMIC AGENTS

At the current time, there are no consensus guidelines determining the sequencing of Ra-223 and other systemic agents. In the prespecified subgroup analysis from the ALSYMPCA trial, investigators reported that Ra-223 prolonged median overall survival irrespective of previous docetaxel use.[20] In comparison, in analogous studies leading to the approval of abiraterone acetate and enzalutamide, a benefit was similarly seen in both docetaxel-naive and postdocetaxel settings. Interestingly, when comparing HRs for death studies utilizing these next-generation antiandrogens to that of Ra-223, the margin of benefit seems to be similar, with HRs in the range of 0.63–0.75.[22-25] Thus, it appears even when comparing systemic therapies with distinct mechanisms of action; clinical benefit is independent of docetaxel exposure.

COMBINATION TREATMENT

The use of concurrent cytotoxic therapy and radioisotope treatment has previously been used with earlier-generation radioisotopes. In a randomized phase II study, bone-targeted therapy for advanced prostate cancer using strontium-89 plus doxorubicin weekly was associated with improved survival versus doxorubicin alone. By targeting the primary tumor as well as the metastatic niche, a synergistic treatment response was achieved. An approach combining cytotoxics with Ra-223 could be even more promising due to lesser toxicity with alpha-emitters.

Next-generation antiandrogens such as abiraterone and enzalutamide appear to be attractive candidates for combination therapy with Ra-223. In previous studies utilizing abiraterone and enzalutamide in the prechemotherapy setting, no significant hematological toxicity was reported.[23,25] Recently, in a single-institution retrospective study, concurrent administration of Ra-223 and next generation antiandrogen therapies appears to be well tolerated with similar toxicities to standard administration of Ra-223 alone.[26] Patients in this cohort were a high-risk, heavily pretreated group with advanced metastatic disease and significant marrow burden. Despite these risk factors, hematologic toxicity was modest and was in the range expected for this risk group based on the previous trials.

Additional studies investigating the combination of Ra-223 with immunotherapy are currently underway.[27] In one hypothesis-generating study, investigators found that T-cell PD-1 expression can be modulated by the use of Ra-223, suggesting possible usage with PD-1 inhibition.[28]

ONGOING TRIALS

Currently, there are a number of trials investigating the use of concurrent antiandrogen and radioisotope treatment. In

one Phase 1/2a clinical trial, patients with mCRPC and bone metastases were either given docetaxel alone versus Ra-223 plus docetaxel.[29] Initial toxicity results were encouraging, with favorably declines in PSA and alkaline phosphatase favoring the combination group. In another study, an international early access program registry trial investigated the effects of concomitant medication on overall survival in mCRPC.[30] Interestingly, in patients receiving Ra-223, survival appeared to be better in those treated concomitantly with denosumab or abiraterone.

MOLECULAR IMAGING IN PROSTATE CANCER

A growing emphasis in the molecular imaging of prostate cancer has increasingly focused on radioisotope-based imaging of prostate-specific membrane antigen (PSMA), a protein frequently overexpressed in prostate cancer.[31] PSMA is an attractive target due to its correlation with a number of known prognostic factors in the development of castration-resistant disease.[32] The first and only FDA-approved molecule in this regard is indium-111 capromab pendetide (ProstaScint®; Cytogen Corporation, Princeton, NJ, USA), which is a radiolabeled monoclonal antibody directed to the PSMA receiving FDA approval in October 1996. Indications for use include its use as an imaging agent for the staging of newly diagnosed patients who are at a high risk for soft tissue metastases as well as for the restaging of postprostatectomy patients with a rising PSA level. However, routine use of this agent did not become widely adopted due to a number of factors related to the logistics of its application.

Recently, a number of next-generation radiotracers targeting PSMA have become available. A number these have been increasingly utilized for both diagnostic and therapeutic purposes including Ga-68, F-18, Tc-99m, Lutetium-177 (Lu-177), and I-131. Of these available radioisotopes, Ga-68 may be a particularly promising candidate due to its high spatial contrast from targeting the extracellular domain of PSMA.[33] In particular, the ability to detect occult lymphadenopathy may be a unique application with Ga-68-based diagnostics.[34] Detection of recurrent prostate cancer lesions before salvage lymphadenectomy has also been demonstrated to be more accurate with Ga-68-based diagnostics[35] and ability to detect disease in the setting of low PSA values makes it suitable in settings with limited prognostic information.[36]

Therapeutic targeting of the PSMA protein has been a logical extension of PSMA-directed-radioisotopes as a possible treatment strategy. The increasing development of theranostics has led to the use of radionuclides with both diagnostic and therapeutic capabilities. Radiolabeled Lu-177 has been particularly been a focus of development due to its favorable physical properties including emission of short-range. Beta particles as well as gamma emission, resulting in less marrow toxic dosing than yttrium-based therapies.[37] A recent Phase II study demonstrated accurate targeting of known sites of disease in patients with castrate-resistant prostate cancer with a dose-dependent reduction in PSA in approximately two-third of patients.[38] Furthermore, Lu-177-based radioisotopes have several characteristics that make it an attractive therapeutic including high affinity to PSMA, long tumor retention time, as well as low kidney uptake and favorably excretion kinetic.[39] A growing number of experiences have shown favorable oncologic responses with minimal toxicities, making development in this arena an exciting area of interest.[40]

CONCLUSIONS

The use of modern radioisotopes in selected patients with mCRPC is associated with improvements in overall survival, pain control, and QOL. Additional research is currently underway comparing the integration of radioisotopes with novel systemic agents.

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Conflicts of interest
Robert Den is on the Advisory Board for Bayer Pharmaceuticals.

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