

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Optimal Use of Radium-223 in Patients With Metastatic Castration-Resistant Prostate Cancer



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H&O What is the treatment protocol for patients with mCRPC?

DG An exciting aspect of the field today is that there are many options for the management of patients with metastatic castration-resistant prostate cancer (mCRPC). Treatment will vary depending on the patient's life expectancy, his functional status, and the aggressiveness of the disease. We are still learning how to optimize the sequence and combination of therapies for different types of patients. Here are 2 examples. A patient with slowly progressive disease develops mCRPC after 10 years of treatment with local therapy and hormonal therapy. He has low-volume, asymptomatic disease. This type of patient will receive monotherapy given in a sequential approach, perhaps starting with sipuleucel-T (Provenge, Dendreon) and then moving to the hormonal therapies abiraterone (Zytiga, Janssen) and enzalutamide (Xtandi, Astellas/Medivation). A sequential monotherapy approach is appropriate for patients with indolent disease, low tumor burden, and no or minimal symptoms. Some patients have such a minimal burden of disease that treatment consists of androgen-deprivation therapy. When patients start to develop more burdensome disease, we will add or switch to cytotoxic therapies, such as radium-223 (Xofigo, Bayer) or the chemotherapies docetaxel or cabazitaxel (Jevtana, Sanofi/Genzyme).

There is also a group of patients with a much more accelerated disease course. They might present with metastatic disease at diagnosis or rapidly progress through hormonal therapy within a year or 2. These patients typically have a more accelerated course after they develop castration-resistant disease, as well. They are usually treated

with combination approaches, such as sipuleucel-T and hormonal therapy. If such a patient is symptomatic, treatment might start with a secondary hormonal therapy, such as enzalutamide or abiraterone, in combination with radium-223. If the patient has visceral disease, there might be a quick switch to docetaxel-based chemotherapy or even platinum-based chemotherapies. We frequently screen tissue samples from these patients to identify DNA damage repair alterations. Combination approaches are suitable for patients with mCRPC who are likely to die of their disease in the next 2 to 3 years and who have a good functional status, regardless of their age. In these patients, I move from one treatment to another when I see indications of functional status changes, even those that are relatively subtle. I do not wait for dramatic changes in scans or symptoms.

These settings are the 2 extremes. There are many cases in between, in which treatment might switch from monotherapy to a combination approach.

H&O What factors impact the selection of treatment?

DG More quantitative measures are needed to predict the course of therapy. In retrospect, it is clear whether a patient's disease is accelerated or indolent, but this distinction can sometimes be difficult to make in real time if things are changing. In this setting, biomarkers are very helpful. Clinical biomarkers that can be used to predict survival include anemia, elevated lactate dehydrogenase, and elevated alkaline phosphatase. Measurement of circulating tumor cells is not common, but it may return to practice with the opportunity to evaluate

for androgen-receptor splice variant 7 messenger RNA (AR-V7) and other prognostic, and maybe even predictive, markers. This area could be very helpful. Molecular imaging, evaluating markers such as fluorodeoxyglucose uptake, novel positron emission tomography imaging, and expression of prostate-specific membrane antigen could also have therapeutic and prognostic implications. There are several opportunities now to evaluate molecular imaging.

Another marker is the burden of disease, bone disease in particular. Bone disease can impact quality of life and limit a patient's tolerance to therapy. It is important to pay attention to the presence of bone disease, and whether it changes. Some patients will have accompanying symptomatic skeletal events, which can also have significant prognostic implications. These factors can help distinguish more accelerated, aggressive disease from slower disease courses.

H&O How common are bone metastases?

DG Bone is by far the most common site of metastasis in mCRPC. It is frequently seen early in castration-resistant disease, and it is often the first site of metastatic disease. It is critical to look for bone metastases and to assess the burden. Some patients develop burdensome disease in the bones without any evidence of tumor burden outside of the skeleton.

Patients can develop complications from skeletal metastases early in the course of mCRPC. These complications are an important way to identify disease that could be lethal. It is necessary to target the bone environment early, before that lethal disease becomes untreatable. We try to recognize early on those patients whose bone disease will become burdensome or problematic.

H&O What are the symptoms in patients with mCRPC and bone metastases?

DG Osseous metastases can lead to pain and many other symptoms. In mCRPC, symptoms can progress slowly. Many of these patients have been receiving hormonal therapy for years, and most are older. It can be easy to attribute relatively subtle symptoms to hormonal therapy and age rather than bone metastases. Symptoms such as fatigue, weakness, decreased functional status, neuropathy, and achiness can be related to the disease burden in the bones. There may be decreased appetite and weight loss. The absolute percentage of weight loss might be minimal, at 3% or 5%, but this could translate to 10 or 15 pounds in a larger person. In a patient receiving hormonal therapy, weight loss is generally not loss of body fat but of muscle, leading to more frailty, which is probably the

most common limiting factor when selecting treatments to maintain quality of life and prolong survival.

Therefore, it is important to recognize that pain is by no means the only symptom that patients develop from osseous metastases. Some of the other symptoms can have a relatively slow onset. Typically, if you ask a patient to compare how he feels today vs 6 months ago or a year ago, there will be a change. This signals to me that the symptoms are probably not from age or hormonal therapy, but rather the disease burden.

H&O What are the benefits to using radium-223 in patients with bone metastases?

DG There are several treatment options for patients with castration-resistant disease, and a strong benefit is that they have different mechanisms. Radium-223 specifically targets the bone microenvironment around the tumor to release radioactive alpha particles. This targeted alpha therapy is able to kill cancer cells agnostically, meaning it is effective regardless of the underlying genetics or heterogeneity of the disease. It does not matter whether the tumor produces prostate-specific antigen (PSA) or not; whether the tumor is anaplastic, neuroendocrine, or neither; whether there is DNA damage repair or pathway alterations; or whether there is loss of *PTEN*, *TP53*, or other tumor suppressor genes. None of these factors protect cancer cells from the double-stranded DNA damage caused by the alpha particle released by radium-223. Radium-223 is therefore a very effective therapy in patients with prostate cancer, and probably other cancers. The key limitation to radium-223 is that its impact is limited to osteoblastic sites of disease. In prostate cancer, however, this limitation is minor because at least 80% of patients have multiple sites of osseous metastatic disease.

We are learning that the earlier radium-223 is used, the better the tolerance. That is true of other therapies as well, but in this case, it is related to the delivery of the drug. If a patient has tumor burden that is spread throughout the marrow, there will be a higher uptake of radium-223 into that marrow. Consequently, there will be more myelosuppression, which, along with gastrointestinal (GI) toxicity, is the most common toxicity associated with radium-223. The way to optimize the effectiveness of radium-223—which requires completion of 6 doses administered throughout a 5-month course—is to initiate therapy before the tumor burden limits tolerance. The best time to administer radium-223 is when patients are beginning to have symptoms associated with their cancer and have an osseous tumor burden at 2 or more sites.

H&O How do you typically assess symptomatic progression?

DG When assessing symptomatic progression, it is important to consider not just pain, but how the patient feels in general. An entire review of systems is needed. A key to symptom assessment is a longitudinal history taken from multiple sources. In my practice, I obtain as much or more information from speaking with the nurses and spouses, and from patient-reported symptom tools, than I do from directly talking with the patient alone. I use information from those other sources to then directly ask the patient in-depth questions about his symptoms.

In the chemotherapy-naïve setting, phase 3 studies of abiraterone or enzalutamide, such as PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naïve Patients With Progressive Metastatic Prostate Cancer) and COU-AA-302 (Abiraterone Acetate Plus Prednisone Versus Placebo Plus Prednisone in Chemotherapy-Naïve Men With Metastatic Castration-Resistant Prostate Cancer), showed that changes in patient-reported outcome occurred on average at approximately the same time as increases in PSA. (The median time to PSA progression was approximately 11 months for the treatment arms in both of these studies.) This finding suggests that a rising PSA level should be an indicator to ask patients about their symptoms and to obtain an in-depth history. At this point, it is unlikely that new symptoms are caused by the treatments; they are probably indicators of disease progression. Therefore, a rise in PSA offers a critical opportunity to question the patient about symptoms.

H&O How important is it to initiate radium-223 early in mCRPC?

DG Data from the ALSYMPCA trial (Alpharadin in Symptomatic Prostate Cancer) suggested that patients who completed all 6 doses of radium-223 had the greatest benefit. The point might be raised that these patients were the most stable and so would live the longest, but they also benefited the most in other ways. It is critical to use radium-223 early in the treatment course, not just so that it has time to work, but because early administration will help patients tolerate treatment and get through all 6 doses with a good functional status and quality of life. When I consider initiating treatment with radium-223, it is generally not for symptom palliation. Symptom palliation can be achieved with appetite stimulants, pain medication, or even a spot dose of palliative external beam radiation. I generally use radium-223 for the survival benefit. Many of the early symptoms are so mild that they do not require palliation, but they act as an indicator that treatment with radium-223 should be considered. The key is to consider use of radium-223 for the survival benefit and to administer it as a one-time course early in the natural history of bone metastases, when the patient

has a much greater likelihood of completing all 6 doses and maximizing the survival benefit.

H&O What are the safety considerations for radium-223?

DG Radium-223, whether administered by itself or in combination with other agents, is very well tolerated and has a relatively limited side effect profile. The side effects are directly related to the delivery and exposure of the drug. The drug is given intravenously, and it quickly binds to bone sites where there is osteoblastic activity. It is essentially a calcium mimetic, and will bind to those areas of the body that calcium does. After binding, radium-223 releases its radiation throughout 10 to 14 days on a very limited field. Because penetration is limited, the toxicity is primarily associated with bone uptake, and usually manifests as limited myelosuppression. Patients with a limited number of bone metastases may not develop any myelosuppression at all. Patients with extensive bony metastases can develop more limiting adverse events for reasons beyond just the burden of disease. These patients already have some anemia, thrombocytopenia, lymphopenia, and/or neutropenia associated with their disease. In addition, they may have received prior therapies. Early administration of radium-223 decreases the chance that a patient will have extensive bony metastatic disease.

Radium-223 can be associated with GI toxicity, particularly in patients with preexisting GI issues. Patients without preexisting GI toxicity tend to tolerate treatment well. The GI toxicities are associated with the clearance of the drug. What is not bound to the bone is cleared primarily through the liver or biliary system and exits via the GI tract. Patients can experience reflux, diarrhea, or constipation. For the most part, adverse events tend to be grade 1, or maybe grade 2 for a limited period. They depend on the timing of treatment and the extent of disease.

Another benefit to radium-223 is that it has no drug interactions. It can be combined with different oral agents and other treatments. Radium-223 is given with hormonal therapies, including enzalutamide and abiraterone, a combination shown to be safe and tolerable. Radium-223 can be given with chemotherapy, although that is not the typical use. Studies of radium-223 and docetaxel have shown that myelosuppression is not a primary concern. Ongoing studies are evaluating this combination. Unlike beta emitters or other forms of radiotherapy, radium-223 does not require a leaded or shielded room or for patients to remain isolated from others. There is no risk of penetrance through the skin to other at-risk populations (eg, children, or women who are pregnant or breastfeeding).

H&O In what settings might radium-223 be used in combination with other therapies?

DG I most frequently combine radium-223 with abiraterone, prednisone, or enzalutamide. Combining radium-223 with hormonal therapies is very helpful, but the timing can be tricky. Among patients who are symptomatic at presentation, it makes sense to add radium-223 to abiraterone or enzalutamide. Among patients treated with abiraterone or enzalutamide who have bony metastatic disease, a rise in the PSA level corresponds to the development of subtle symptoms, although scans may not show radiographic progression. Traditionally, these patients will continue treatment with hormonal therapies; we might switch from abiraterone to enzalutamide and vice versa. In addition, I view this as a good time to add radium-223, which can begin to target minimally symptomatic disease before it becomes too burdensome. It is important to know that use of radium-223 in these early settings does not limit chemotherapy options later. When the tumor burden is advanced, usually a choice must be made between radium-223 or chemotherapy; both treatments are generally not used together.

We are conducting a clinical trial of radium-223 in combination with sipuleucel-T, a particularly interesting setting because patients treated with sipuleucel-T have minimal symptoms. The cytotoxicity associated with radium-223 may have a stimulatory effect, potentially releasing neoantigens and other proteins that the immune system could recognize in conjunction with those elicited by sipuleucel-T. Sipuleucel-T causes the immune system to recognize prostatic acid phosphatase or the fusion protein with granulocyte-macrophage colony-stimulating factor, which leads to the creation of antibodies as well as cellular disease responses or immune responses. Radium-223 can also be given with concomitant external beam radiotherapy. Concomitant external beam radiotherapy was allowed in the pivotal ALSYMPCA study and is an important consideration for patients with a large symptomatic skeletal event. There is no need to delay radium-223 treatment in these cases.

H&O Who is the ideal patient for radium-223?

DG The ideal patient for radium-223 is one who has just begun to develop bony metastatic disease burden. He is minimally symptomatic and typically not receiving treatment with narcotics. He has no more than 5 or 6 bone metastases, but some lesions look sizeable enough that they could result in symptomatic skeletal events in the future. The patient does not have visceral disease or lung or liver metastases. I might treat this patient with additional agents, such as enzalutamide or abiraterone. The phenotype

of the cancer is probably somewhat more aggressive than usual. The patient may have been diagnosed 5 or 6 years earlier and has progressed through the standard local and hormonal therapies. The patient may have presented with limited metastatic disease, and now has progressed into the castration-resistant disease setting.

In addition, the ideal patient for radium-223 will be able to complete the treatment course to maximize the benefit. His life expectancy is long enough that he can receive treatment with chemotherapy and other approaches.

When possible, I like to biopsy tissue from these patients, and that is difficult after treatment with radium-223. I might obtain computed tomography-guided biopsies of the bone marrow, pelvic lesions, small lymph nodes, or even local disease. The presence of DNA damage repair alterations or other genetic targets does not impact treatment with radium-223, but it may affect the choice of other subsequent therapies, including some novel agents and immunotherapies.

Although these patients may have other options, such as hormonal therapy, chemotherapies, or even investigational mutational-based approaches, radium-223 has a role in helping to extend survival, particularly when the bone environment is thought to drive progression. An ideal patient for radium-223 has metastatic disease in the bone that manifests early or has evidence of progression of metastatic disease burden in the bones, with symptoms that may be minimal.

H&O How do you optimize coordination of care across the referring clinician to the injecting clinician?

DG The best way to optimize multidisciplinary care is for different specialists to talk to each other. This can be facilitated in several formal or informal ways. At Duke, we have regularly scheduled tumor boards where we informally present recent cases from our clinics to obtain feedback, advice, and consultation. These meetings include pathologists and radiologists, who provide insight into how to interpret images. In addition to these tumor boards, we also maintain close communication, via phone, e-mail, or texts, to establish common practice patterns. It is important to share with other providers, such as urologists and radiation oncologists, the goals of care, including maximizing overall survival, quality of life, and specific life milestones that the patient and primary oncologist have established together.

Contact with community physicians is also important. I discuss cases with several oncologists and urologists in the community. A vital role of academic medical centers is to be a resource for community physicians.

H&O How do you describe how radium-223 works to your patients?

DG It is essential to explain to patients how drugs work. Patients have to believe that the treatment will be beneficial, and this can be enhanced with a better understanding of the treatment's activity. When explaining the mechanism of radium-223, I describe it as a collection of small cannonballs rather than a broader systemic therapy. Radium-223 is very targeted and focal to the tumor, and it has a limited range. Depending on the patient, I then might explain some of the nuclear physics behind the treatment.

It is also important to explain to patients that treatment with radium-223 is usually not associated with a decline in PSA levels. Some tumor growth outside the field of radium-223 will continue to progress. Some cancer cells may even begin to produce more PSA. A marker that does drop consistently is alkaline phosphatase, which is produced within the bone microenvironment that is targeted by radium-223. Among patients with an elevated alkaline phosphatase, we will monitor these levels.

Patients should be aware that radium-223 may not show an immediate treatment effect. Bone scans do not necessarily change, and some changes are too subtle to quantitate. However, we know that radium-223 is associated with a survival benefit across the population and not just in particular subsets. The majority of patients who receive treatment with radium-223 benefit from it, particularly if they receive all 6 cycles. I encourage patients to understand the mechanism and why traditional measures of disease response are not applicable. When patients receive this information when therapy is initiated, they are much less likely to be frustrated or anxious at the end of the therapy.

H&O Do you have any other clinical considerations when using radium-223?

DG Treatment with radium-223 takes some coordination. In general, the physicians who select this treatment are not the same ones who order it and administer it. Medical oncologists and urologists generally do not have a nuclear medicine license, which is needed to administer radium-223. Treatment with radium-223 therefore requires a multidisciplinary approach. Medical oncologists must partner with radiation oncologists and nuclear medicine physicians.

My patients receiving treatment with radium-223 make monthly office visits, so I can oversee management and address any symptoms. Signs of disease progression

might lead to reassessment. Many of these patients still need our attention and care.

It is important to recognize that radium-223 does not replace other therapies or clinical trials, but it provides a unique way to improve survival. The key decision for oncologists who treat patients with advanced CRPC and osseous metastatic disease is not if we will treat with radium-223, but when.

Disclosure

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Suggested Readings

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