CLINICAL UPDATE

Advances in the Treatment of Prostate Cancer

When to Initiate Treatment With Radium-223 in Patients With Metastatic Castration-Resistant Prostate Cancer

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H&O How many patients with castration-resistant prostate cancer (CRPC) develop bone metastases?

NS Data from many phase 3 clinical trials, inclusive of both retrospective and prospective analyses, as well as prostate cancer registries from various countries, suggest that more than 90% of men who die of CRPC have bone metastases. Prognosis is significantly worse among these patients. A study from 2010 showed that 5-year survival was 3% among prostate cancer patients with bone metastases compared with 56% in patients without bone metastases. Disease often progresses despite hormonal therapy (see the figure).

H&O How prevalent are symptoms in these patients?

NS This question raises an important point about how to define and describe symptomatology. It seems likely that symptoms are more prevalent than reported.

Pain is the most common symptom, and historically, the symptomatology of bone metastases was considered binary: pain or no pain. However, pain is often elusive. A large survey conducted by the International Prostate Cancer Coalition (IPCC; results posted at MenWhoSpeakUp.com) showed that many patients with bone metastases have symptoms they would not describe as bone-related pain. For example, they may experience new-onset difficulties getting into and out of a car. Their sleep pattern may be interrupted by nightly discomfort. They may stop regular activities, such as walking upstairs, hitting a tennis ball, or swinging a golf club, and they may find themselves ingesting increased doses of over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs, acetaminophen, or aspirin. Patients may develop inanition, cachexia, and fatigue, which can be related to tumor burden and bone metastases. Clearly, this symptomatology can decrease quality-of-life metrics.

The recent IPCC survey found that in approximately 50% of men, there was a 7-month delay from the time they recognized their bone symptomatology to the time they discussed it with their clinicians (including both physicians and nurses). Oftentimes, symptoms were noticed by caregivers approximately 3 months before the patients recognized them.

At the same time, and oftentimes counterintuitively, there are patients with large tumor burdens of bone metastases who fail to demonstrate any symptoms. Therefore, symptoms should not be the sole criteria when deciding to proceed with treatment.

H&O What are the treatment options for CRPC patients with bone metastases?

NS The past several years have seen the advent of bone-targeted therapies, such as zoledronic acid (Zometa, Novartis) and denosumab (Xgeva, Amgen), that delay the incidence of skeletal-related events (SREs), such as fracture, need for pain palliation, surgical intervention, and cord compression. These events are not only associated with significant morbidity and quality-of-life issues, but can hasten a patient's death. Radium-223 (Xofigo, Bayer HealthCare) has been shown to significantly delay the development of symptomatic skeletal events. More importantly, radium-223 is a life-prolongation therapy, as shown in the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial, which demonstrated a

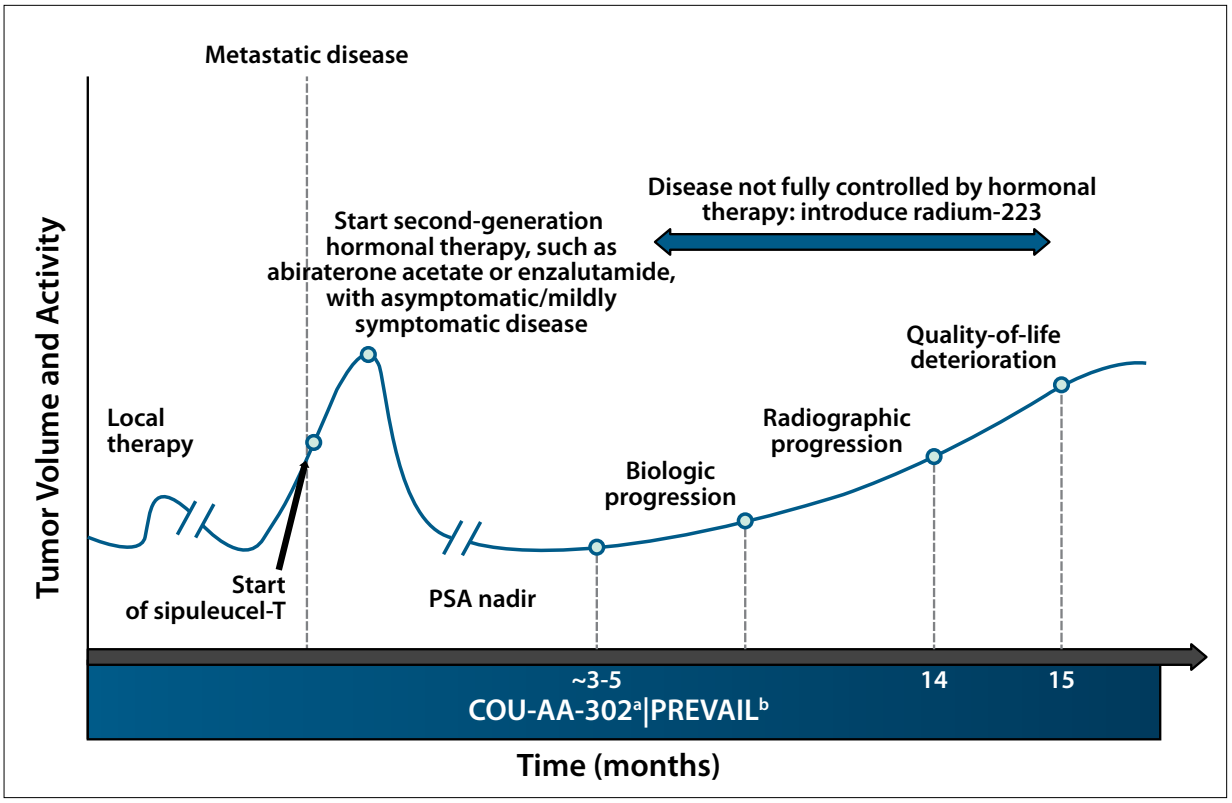

Figure. Disease progression despite hormonal therapy in men with prostate cancer. PSA, prostate-specific antigen. [a]Earliest time point, PREVAIL. [b]Latest time point, COU-AA-302. Data from Ryan CJ et al. *N Engl J Med*. 2013;368(2):138-148. Ryan CJ et al. *Lancet Oncol*. 2015;16(2):152-160. Beer TM et al. *N Engl J Med*. 2014;371(5):424-433. Loriot Y et al. *Lancet Oncol*. 2015;16(5):509-521.

statistically significant improvement for overall survival in the radium-223 treatment arm.

H&O What type of therapy is radium-223?

NS Radium-223 is a radioisotope that emits an α molecule. The earlier-generation radiopharmaceutical agents emitted β/ϒ molecules, which are, simply stated, much smaller than α molecules. The advantage of the larger α particle is that it has a much shallower penetration at the level of the cortical bone, and thus is less likely to penetrate the marrow and impact myeloid proliferative tissues. It is therefore associated with a reduced risk of marrow toxicities, such as neutropenia or thrombocytopenia. Historical radiopharmaceuticals, such as strontium and samarium, have much deeper penetration and, consequently, much higher toxicity profiles, primarily involving myelosuppression. Of note, neither samarium nor strontium demonstrated an overall survival benefit in a phase 3 trial. They have been used for symptomatic pain control among patients with highly refractory, widespread bone metastases.

The placebo-controlled, double-blind, prospective, randomized ALSYMPCA trial of radium-223 included more than 900 patients with CRPC who had received chemotherapy and progressed (approximately 55%) or did not receive docetaxel because they were ineligible for it or declined it (approximately 45%). Therefore, the population included a mix of prechemotherapy and postchemotherapy patients. The study population reflects the multimodality approach used at this point in the treatment course. Patients were permitted to receive treatment with standard-of-care therapy. In this global trial, these therapies included oral antiandrogens, such as bicalutamide (Casodex, AstraZeneca); the androgen biosynthesis blocker ketoconazole; corticosteroids; estrogens; and concomitant external-beam radiation therapy for palliation of bone pain. Distribution of these previous therapies was well-balanced between the treatment arms.

Patients were randomly assigned, in a 2:1 manner, to receive an infusion of radium-223 or saline. Radium-223 was administered every 4 weeks for a total of 6 infusions (for a treatment course of 6 months). The infusion was made through a peripheral intravenous line, and it lasted 45 to 60 seconds. There was no premedication or postmedication requirement.

The study showed a median overall survival benefit of 3.6 months, with a hazard ratio of approximately 0.7 demonstrating a 30% improvement at most time points among patients treated with radium-223. There was also a delay in the development of symptomatic skeletal events. That being said, it is important to emphasize that radium-223 is the only radiopharmaceutical to demonstrate a life-prolongation effect in the CRPC population. Radium-223 is the most recently approved life-prolonging therapy for CRPC, joining docetaxel, sipuleucel-T (Provenge, Dendreon), abiraterone acetate (Zytiga, Janssen), enzalutamide (Xtandi, Astellas/Medivation), and cabazitaxel (Jevtana, Sanofi-Aventis).

Rates of myelosuppression associated with radium-223 were slightly higher among patients who had previously received chemotherapy, at 4% vs 1%. Among the radium-223 patients who had not received previous chemotherapy, rates of grade 3/4 neutropenia and thrombocytopenia were less than 5%.

Data from the ALSYMPCA trial show that there is now a first-in-class radiopharmaceutical therapy that not only prolongs survival, but does so with a mechanism of action that is distinct from that of the other agents approved for CRPC. Radium-223 creates an apoptotic effect by enhancing double-stranded DNA breaks at mineralization sites in the bone metastases. It does not target the androgen/androgen-receptor axis, and it does not inhibit tubulin (like taxane therapy does). Radium-223 is easy to administer and has a very good tolerability profile, both as a single agent and in combination with other therapies. Throughout North America, Europe, Scandinavia, and other parts of the world, expanded access programs combining radium-223 with abiraterone acetate or enzalutamide raised no safety signals beyond those expected when giving these therapies in sequence.

The full course of radium-223 therapy is 6 infusions, 4 weeks apart. In the expanded access program, patients who received at least 5 infusions did much better than patients who received 1 to 4 infusions. In the ALSYMPCA trial, more than 90% of patients received the full course of therapy. That high rate is typical of a clinical trial, where there is greater fidelity to protocol adherence, but more patients are now receiving the complete course in clinical practice as well.

It is important for patients to begin treatment with radium-223 before their performance status deteriorates and they require chemotherapy. After chemotherapy, patients may have a worsening tumor burden, may be more immunosuppressed, and may be less able to tolerate any type of therapy. When I began treating patients with radium-223, I reserved it for those who had already received chemotherapy. Currently, approximately 90% of my patients receive radium-223 before chemotherapy. Almost invariably, I administer radium-223 concomitantly with either abiraterone acetate or enzalutamide.

That being said, in other parts of the world, combinatorial therapies might not be accessible or reimbursed. In this situation, I would consider giving a course of radium-223 after abiraterone acetate or enzalutamide in a patient who does not have an initial decline in prostate-specific antigen (PSA) levels. An escalation of PSA after an initial response to novel oral hormonal therapy may indicate that the patient has developed resistance to these agents. For these patients, radium-223 should be considered because of its ease of administration, excellent tolerability, and unique mechanism of action.

Radium-223 must be administered by a clinician licensed by the Nuclear Regulatory Commission. Invariably, the clinician will be a radiation oncologist or a nuclear medicine radiologist, augmenting the multidisciplinary approach to CRPC therapy, which is always in the patient's best interest. Radium-223 can be administered within a hospital or a freestanding clinic.

H&O Which type of patients are candidates for radium-223?

NS A post-hoc analysis of ALSYMPCA evaluated outcome according to prior treatment status. Among patients who had not received chemotherapy, the median overall survival was 16.1 months in the radium-223 arm vs 11.5 months in the placebo arm. Among patients who had received previous treatment with docetaxel, median overall survival was 14.4 months in the radium-223 arm vs 11.3 months in the placebo arm. The improved outcome before chemotherapy has led me to now discuss use of radium-223 with my patients with M1 CRPC who are experiencing symptoms from their bone disease. As I mentioned earlier, this symptomatology can encompass more than pain. In the ALSYMPCA trial, approximately 55% of the patients were receiving narcotic analgesics.

H&O Is the PSA level helpful for monitoring patients receiving radium-223?

NS Throughout the ALSYMPCA trial, there were not many decreases in PSA. It is not surprising that radium-223 does not impact PSA because it does not target the antigen receptor, which is responsible for the PSA gene and, ultimately, development of the PSA protein. ALSYMPCA did show a dramatic decline in alkaline phosphatase levels among patients with elevated bone alkaline phosphatase, a surrogate for bone tumor burden. When I administer radium-223 to patients with a baseline elevation of alkaline phosphatase, I explain that we will monitor this level because it can be a measure of treatment efficacy.

H&O Are there any guideline recommendations regarding radium-223?

NS Guidelines from the American Society of Oncology, European Society for Medical Oncology, European Association of Urology, American Urological Association, and National Comprehensive Cancer Network have incorporated radium-223 as demonstrating level 1 evidence for use in CRPC patients with bone metastases who have or have not received taxane-based chemotherapy. In the NCCN guidelines, the use of radium-223 after the first novel hormone is a level 1 recommendation. Radium-223 is not for patients with visceral metastases.

H&O Does any type of prior therapy impact the outcome with radium-223?

NS There does not appear to be a prior therapy that would preclude the use of radium-223. Radium-223 is approved as a course of therapy consisting of 6 cycles. It is not approved for any additional cycles, although they are being studied. Future trials may show that additional cycles or even higher dosages may be of further benefit. Ongoing studies are evaluating additional combinatorial strategies. The only concomitant agents that are contraindicated in the labeled approval for radium-223 are taxane-based chemotherapies.

H&O Do you have any recommendations regarding the clinical use of radium-223?

NS Any clinician who has dedicated his or her practice to treating men with metastatic CRPC should be knowledgeable about radium-223, as well as about the other approved CRPC therapies. Radium-223 has been an outstanding addition to the treatment armamentarium for these patients. I consider the use of radium-223 in combination with enzalutamide or abiraterone acetate, as well as after these agents in patients who experienced biological progression (as evidenced by PSA elevation from their nadirs).

We are moving toward an understanding that multimodality therapy—the right therapeutic for the right patient at the right time—is ideal. The role for radium-223 becomes even more interesting as we develop greater insights into specific biomarkers, such as somatic or germline mutations targeted by poly ADP ribose polymerase (PARP) inhibitors. In addition, the distinct mechanism of action of radium-223 might be beneficial in patients with splice variants, such as androgen-receptor splice variant 7 messenger RNA (AR-V7), that might render novel oral hormonal agents less advantageous.

Disclosure

Dr Shore has served as an advisor or consultant for Astellas Pharma, Bayer HealthCare Pharmaceuticals, Dendreon Corporation, Ferring Pharmaceuticals, Janssen Pharmaceuticals, Medivation, Millennium Pharmaceuticals, and Sanofi.

Suggested Readings

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