

## Treatment Options for Patients With Prostate Cancer Who Develop Metastatic Disease After Hormonal Therapy



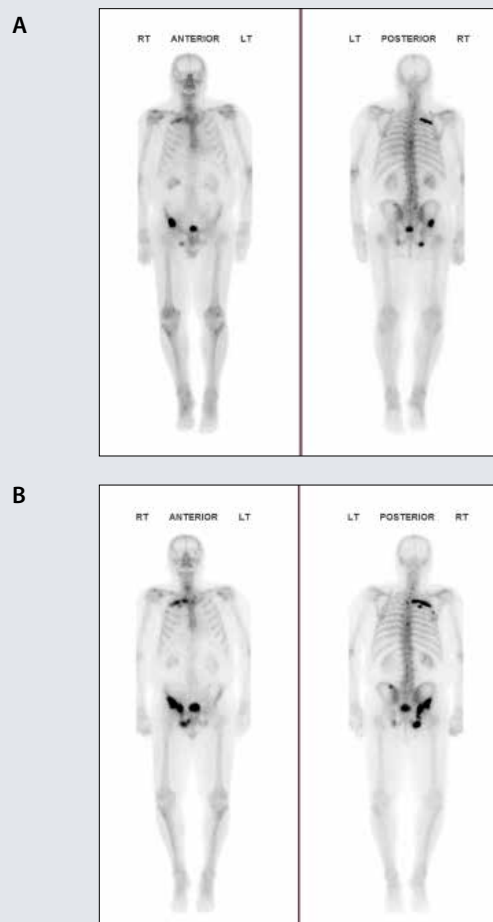
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### Case

The patient is a 66-year-old man in good cardiovascular health. He has a family history of prostate cancer. He presents with fatigue and minor discomfort in his lower back. He had not undergone previous prostate-specific antigen (PSA) testing. His first PSA test shows an elevated level of 7 ng/mL. Imaging reveals 3 bone metastases: 2 in the pelvis and 1 in the right posterior rib (Figure 1A). He has no visceral disease. His Gleason score is 4+4. The patient is diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC), and he begins treatment with abiraterone acetate (Zytiga, Janssen) plus prednisone. A dual X-ray absorptiometry (DEXA) scan reveals an index T-score of  $-1.5$  in his femurs. Based on the moderate risk for fracture, he begins treatment with androgen deprivation therapy (ADT) plus zoledronic acid.

Three months later, the patient's PSA is undetectable and his pain has resolved. At 18 months, he presents with increased discomfort in his lower back and increased fatigue. His PSA level has risen from undetectable to 3 ng/mL in the past 3 months. Repeat imaging reveals a new lesion in the lower spine. Minor lymph node involvement is also detected. Based on the increase in PSA and the new lesion, the patient is diagnosed with metastatic castration-resistant prostate cancer (mCRPC). Treatment with abiraterone acetate is discontinued. The patient begins treatment with radium-223 (Xofigo, Bayer) and receives 6 cycles. His PSA level rises to 10 ng/mL. He has no reported discomfort in the lower back. A repeat bone scan shows stable disease. The patient begins treatment with enzalutamide (Xtandi, Astellas/Pfizer). After an initial PSA decline on enzalutamide, his PSA reaches a nadir of 3.5 ng/mL after 3 months of treatment.

At 33 months (6 months on enzalutamide), the patient presents with moderate fatigue. His PSA level is now 20 ng/mL. Imaging reveals osseous metastases that increased in size and number, but no metastases beyond the bone (Figure 1B). His hemoglobin score is 11.5 g/dL, and his alkaline phosphatase level is 150 U/L. The remainder of his blood counts are within normal limits. Treatment with enzalutamide is discontinued. The patient receives



**Figure 1.** A, The patient's first imaging scan reveals 3 bone metastases: 2 in the pelvis and 1 in the right posterior rib. B, At 33 months after diagnosis, imaging reveals osseous metastases that increased in size and number, but no metastases beyond the bone.

6 cycles of chemotherapy with docetaxel and prednisone. He remains clinically stable. Chemotherapy leads to side effects such as fatigue, anemia, and grade 1 peripheral neuropathy.

**H&O** How is mHSPC defined?

**DG** The definition of mHSPC has 2 components. First, the disease is defined by the presence of metastasis, which is usually evident on a bone scan or computed tomography scan. These lesions do not have to be measurable or confirmed with a biopsy. However, they should be consistent with the pattern associated with prostate cancer. For atypical sites of disease, confirmation with biopsy is recommended.

The second half of the definition is more complicated. Patients who have not received previous hormonal therapy for metastatic disease are assumed to be sensitive to treatment. Among patients with prior exposure to hormonal therapy, those with recovery of testosterone in the setting of a rising PSA (as evidence of disease progression) are deemed hormone-sensitive. The precise testosterone thresholds in this setting are not established, but in general, levels higher than 150 ng/dL are considered recovered.

The definition of mHSPC is therefore broad. There are no minimums or limits to the amount of prior hormonal therapy, and there are no restrictions on the metastatic sites.

**H&O** What factors influence your selection of abiraterone acetate vs chemotherapy in patients with mHSPC?

**DG** Both of these treatments (when combined with standard ADT) have improved overall survival in unselected patients.<sup>1,2</sup> However, disease volume can help guide treatment. For patients with low-volume disease, I generally prefer abiraterone acetate because the clinical benefit of this approach remains constant regardless of the disease volume. In contrast, up-front use of docetaxel chemotherapy has a robust clinical benefit in patients with high-volume disease (defined as  $\geq 4$  bone lesions or the presence of visceral disease). In a subgroup analysis of a randomized trial, the benefits of docetaxel chemotherapy appeared to be less significant among patients with low-volume disease.<sup>3</sup> For patients with high-volume disease, I prefer docetaxel with the option of adding novel anti-hormonal therapy, such as abiraterone acetate or enzalutamide. Study results, expected later this year, may clarify the benefit of combining these approaches up front in patients with a high volume of disease.<sup>4,5</sup>

**H&O** In your practice, how quickly do patients with mHSPC progress to mCRPC?

**DG** The use of abiraterone acetate in the setting of

mHSPC is relatively new, based on data presented in 2017.<sup>1</sup> I therefore do not have too many patients who have progressed through this initial line of therapy in this setting.

Docetaxel chemotherapy has been used in mHSPC since 2015.<sup>2</sup> In general, my experience has been similar to what has been seen in clinical trials of patients with high-volume mHSPC. In my practice, patients develop progressive disease anywhere from 6 months to 2 years following docetaxel chemotherapy.

**H&O** What factors trigger initiation of subsequent therapy after a patient progresses on hormonal treatment in the mHSPC setting?

**DG** Progression from mHSPC to mCRPC is typically defined by a rise in PSA that occurs during treatment with ADT.<sup>6</sup> In some cases, an increase in PSA without radiographic progression would not initiate a change in treatment. Typically, however, a change in treatment is based only on a rise in PSA, regardless of radiographic progression. For patients who remain asymptomatic with low-volume metastatic disease, sipuleucel-T (Provenge, Dendreon) is an option. For patients who are symptomatic or who have substantial radiographic progression, we will consider subsequent cytotoxic therapies, such as docetaxel chemotherapy or radium-223.

**H&O** What do data suggest about back-to-back hormonal therapy?

**DG** Frequently, patients who switch from one hormonal agent to another have no PSA response or just a brief one.<sup>7</sup> In general, after hormonal therapy, I prefer to change to a drug with a different mechanism of action to prevent up-front cross-resistance. Switching to a cytotoxic agent such as docetaxel or radium-223 offers the opportunity to avoid potential cross-resistance. That said, there are cases in which patients have low-volume asymptomatic disease progression and may not require the immediate use of a cytotoxic therapy. When patients have responded to a primary hormonal therapy for a long period, switching to another in-class hormonal agent can lead to disease control in some cases.

**H&O** What are your goals in the management of mCRPC?

**DG** When discussing mCRPC with patients, my colleagues and I convey that the primary goal is to maximize quality of life and survival. We try to maintain a good performance status for as long as possible. To do this may require relatively proactive treatment with

different classes of agents, including novel anti-hormonal therapies; cytotoxic therapies, such as radium-223 and docetaxel; and palliative uses of radiation therapy or surgery. We also counsel patients regarding behavior modifications that can help maintain their functional status, including a healthy diet, adequate exercise, and good sleep hygiene. We monitor patients for disease progression before symptoms. We also monitor patient-reported outcomes to identify changes in quality of life as the disease progresses through CRPC. Thankfully, patients are living longer than ever with this disease state. It is important to recognize, however, that performance status is difficult to reverse once it has declined owing to the disease. Therefore, treating patients to maintain these goals is a priority.

### **H&O** Why was this patient a good candidate for radium-223?

**DG** This patient was a good candidate for radium-223 for several reasons. First, he demonstrated evidence of symptomatic disease early in his course and again when he developed progressive disease during treatment with abiraterone acetate and prednisone. This finding suggests that his bone disease was associated with an inflammatory phenotype and will likely impact his quality of life and performance status in the future. Second, his disease was bone-predominant, with minimal lymph node involvement. Repeat imaging appeared to show that disease progression was limited to the bone environment. Therefore, targeting the bone environment with an agent with a different mechanism of action from hormonal therapy may be beneficial. Third, this patient had a good performance status, and radium-223 is well-tolerated in this setting. The patient was able to receive all 6 doses of radium-223, with minimal effects on his quality of life. He was also able to receive subsequent therapy with chemotherapy following radium-223.

### **H&O** Are there benefits to using radium-223 earlier vs later?

**DG** In general, outcome is improved when patients receive all 6 doses of radium-223.<sup>8</sup> Radium-223 is usually better-tolerated in patients who have a lower tumor burden in their bones. Patients with a good hematologic profile, in particular, are able to maintain radium-223 on schedule, with minimal impact to their blood levels in most cases. In contrast, it becomes difficult to administer all 6 doses of radium-223 to patients with low hemoglobin or platelet counts, who are at higher risk of further decline. Patients who are treated later in their disease course often develop progressive disease that requires

further intervention within the timeframe needed to administer all 6 doses.

### **H&O** What is your advice to peers regarding the sequencing of radium-223 in chemotherapy?

**DG** In my experience, patients tolerate radium-223 better when it is administered early in the disease course, before they have suffered significant cytopenias and when they have less overall tumor burden.<sup>9</sup> Early administration of radium-223 also allows patients to better tolerate subsequent chemotherapy. For patients who present with a mix of substantial soft tissue disease and bone disease, I am more inclined to use chemotherapy first. However, for my patients who have bone-only disease, I typically use radium-223 early in the disease course for the known survival benefit as well as to see if it can impact the long-term control of these disease sites.

### **H&O** What is the hematologic profile of chemotherapy when used after radium-223?

**DG** There are no extensive data on chemotherapy tolerance following radium-223. Limited studies suggest that chemotherapy after radium-223 is well-tolerated and does not lead to additional cytopenias.<sup>10</sup> In my own experience, if radium-223 is given late in the disease course, particularly in patients with a poor performance status and high-tumor burden, then the opportunity to give chemotherapy afterward is limited. Therefore, if I am going to administer radium-223 before chemotherapy, I like to do so early in the disease course.

### **H&O** What factors contributed to this patient's risk of fractures throughout his treatment for prostate cancer, and how can physicians monitor bone health?

**DG** The patient in the case study was treated with zoledronic acid based on his increased fracture risk. Bone loss and fractures can be monitored with DEXA scans. Multiple factors influence the risk of fractures in patients with prostate cancer. Older age is a factor. Many patients with prostate cancer can live 10 years or longer from the time they begin treatment with hormonal therapy. It is important to recognize that nearly all treatments for prostate cancer can increase the risk of bone loss and/or fractures. ADT is a risk factor for bone loss and fractures.<sup>11</sup> The risk of fractures can be increased by novel hormonal therapies, chemotherapy, and prednisone (which is commonly used with both chemotherapy and hormonal agents, such as abiraterone acetate).<sup>12-14</sup> The combination of abiraterone acetate, prednisone,

and radium-223 has been shown to increase the risk of fractures.<sup>15</sup>

It is necessary to begin monitoring of bone health early, based on a patient's baseline risk of fractures when he starts ADT. Patients should undergo periodic monitoring throughout the disease course. It is wise to advise patients of supportive measures to minimize the risk of bone loss and fractures, which include calcium and vitamin D; bone-strengthening agents, such as zoledronic acid and denosumab; and exercise.

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

**DG** I describe radium-223 as a targeted therapy.<sup>16</sup> It is a calcium mimetic that was selected specifically to target bone lesions—in particular, those lesions that take up calcium and phosphate as demonstrated on a technician bone scan.<sup>17</sup> Once taken up into these lesions, radium-223 releases a high-energy radiation that has very short penetrants. It acts similarly to brachytherapy in these metastatic sites, pinpointing radiation into the tumor environment. Precisely how radium-223 kills cancer cells is still under study. However, radium-223 appears to be unselected in killing cells in the tumor microenvironment. Radium-223 therefore has multiple advantages because it is able to kill cells regardless of whether they express the testosterone receptor or have other genetic alterations.

An important point for patients to understand is that because radium-223 is so targeted, it may not lower PSA.<sup>18</sup> The release of radiation is limited to this microenvironment, which may not encompass the cells that create PSA. Levels of PSA may rise, and yet radium-223 may still significantly improve survival and delay deterioration in quality of life. I frequently counsel patients to expect a rise in their PSA levels, sometimes reaching several-fold over the course of the treatment period. This rise should not be interpreted as a sign that radium-223 is not working. In addition, the significance of PSA changes diminishes as prostate cancer advances through the castration-resistant disease state.

### Disclosure

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