CLINICAL UPDATE

Advances in the Treatment of Prostate Cancer

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

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There are 5 life-prolonging therapies for men with metastatic castration-resistant prostate cancer (CRPC): abiraterone acetate (Zytiga, Janssen), enzalutamide (Xtandi, Astellas/Medivation), docetaxel, cabazitaxel (Jevtana, Sanofi-Aventis), and radium-223 (Xofigo, Bayer HealthCare). The phase 3 ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial evaluated the addition of radium-223 or placebo to best supportive care among 921 men with advanced prostate cancer and progressive bone metastases. There was a 30% survival benefit for radium-223 (median, 14.9 months vs 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; *P*<.001; see the figure).[1] Subgroup subanalyses evaluated overall survival according to whether patients had received prior treatment with docetaxel.[2] In patients who had received previous docetaxel, median overall survival was 14.4 months in the radium-223 arm vs 11.3 months in the placebo arm (HR, 0.71; 95% CI, 0.57-0.89; *P*=.003). In patients who had not received previous docetaxel, median overall survival was 16.1 months in the radium-223 arm vs 11.5 months in the placebo arm (HR, 0.75; 95% CI, 0.56-0.99; *P*=.039).

The magnitude of benefit seen with radium-223 is comparable to that seen with the other life-prolonging therapies.[3-7] Most men with metastatic CRPC should receive treatment with all 5 of these agents, although the optimal sequencing and combinations are unknown. Radium-223 is approved for CRPC patients with symptomatic bone metastases and no known visceral metastatic disease, which encompasses most of the metastatic CRPC population. Men particularly suited for treatment with radium-223 include those with metastases in the bone but not elsewhere. However, men with bone metastases and lymph node metastases still stand to benefit from radium-223 and should receive treatment.

Monitoring

Radium-223 is usually extremely well tolerated. In the ALSYMPCA trial, there were more adverse events in the placebo group than the radium-223 group.[1] However, patients receiving radium-223 should be evaluated for toxicities using a complete blood count. Platelet toxicity, although unusual, has occurred. An up-to-date complete blood count should be obtained before each cycle of radium-223. When thrombocytopenia does occur, it typically appears gradually toward the end of a 6-month course of treatment. Recovery from thrombocytopenia can be slow. I usually discontinue treatment in patients with a platelet count of less than 70×10^9/L.

There is no definitive way to measure response to radium-223. Most patients should complete the regimen that has been shown to be effective and well tolerated: 6 cycles, administered once every 4 weeks. This regimen is supported by an analysis of the ALSYMPCA trial, presented at the 2015 European Society for Medical Oncology (ESMO) meeting. The median overall survival was 17.9 months among patients who received 5 to 6 injections vs 6.1 months among patients who received 1 to 4 injections.[8] The prostate-specific antigen (PSA) test is not used to measure response because this level typically continues to rise during treatment with radium-223. When the PSA level does decline, it is usually after 4 or 5 months of treatment, which is too late for assessing response. In contrast, the alkaline phosphatase level almost always decreases during treatment with radium-223. However, alkaline

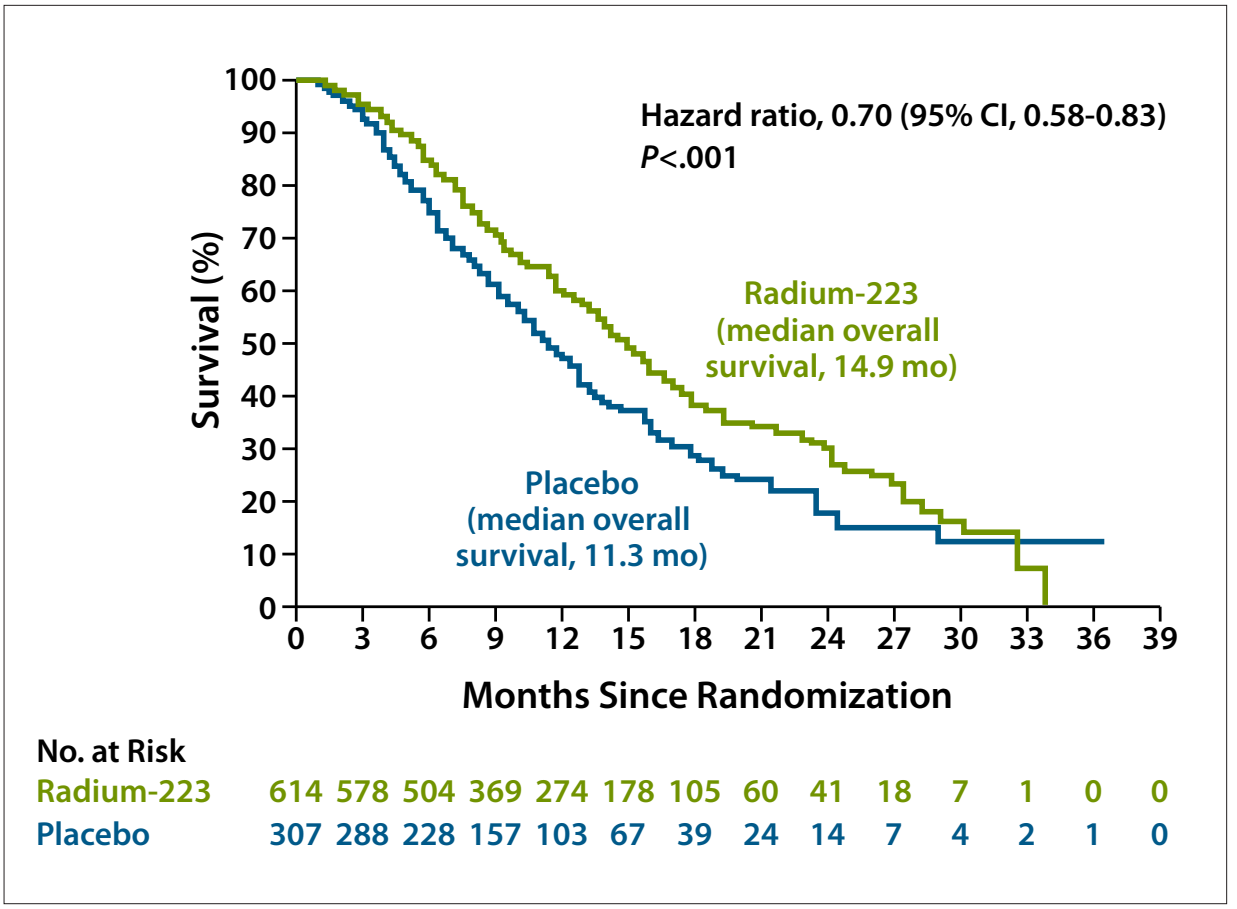

Figure. Overall survival in the ALSYMPCA trial. ALSYMPCA, Alpharadin in Symptomatic Prostate Cancer. Adapted with permission from the *New England Journal of Medicine*. Parker C et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. Volume 369, Pages 213-223.[1] Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

phosphatase cannot be used to measure response because it is not known whether this decrease reflects tumor response or just an effect on bone turnover.

There is the potential for response to be measured with imaging. Conventional imaging modalities, such as bone scans and computed tomography, are unsuitable because they cannot be used to assess bone disease. Diffusion-weighted magnetic resonance imaging is showing promise and might be an option in the future.

When to Initiate Radium-223

A common question is where to use radium-223 in the context of the other life-prolonging therapies. In the ALSYMPCA trial, radium-223 was not used as monotherapy but rather combined with best standard treatment. When the trial was open to recruitment, best standard treatment comprised therapies such as bicalutamide, corticosteroids, and estrogens. The newer hormonal agents were not available. It appears rational to use radium-223 in combination with the current best standard treatments, abiraterone and enzalutamide. In some parts of the world, economic constraints prevent the use of radium-223 in combination with relatively expensive drugs, such as abiraterone or enzalutamide. For example, this combination is not permitted in the United Kingdom.

I use radium-223 in combination with dexamethasone, which is another effective androgen receptor–targeted treatment that is far less expensive than abiraterone and enzalutamide. Dexamethasone given at a dose of 0.5 mg/day is associated with a PSA response rate of approximately 50% and a median duration of PSA response of approximately 12 months.[9] It is superior to other corticosteroids, such as prednisolone. Use of dexamethasone in combination with radium-223 has 2 advantages. First, the decline in PSA often seen with dexamethasone may reassure patients. Second, dexamethasone can treat disease that occurs outside the skeleton, while radium-223 treats the bone metastases. I usually use dexamethasone and radium-223 in combination as first-line therapy for meta-

static CRPC patients with bone metastases. If the patient has progressive disease while receiving dexamethasone, I then switch to abiraterone or enzalutamide.

Typically, I reserve chemotherapy, such as docetaxel or cabazitaxel, for use only after the hormonal agents and radium-223. Patients clearly prefer to initiate treatment with the less-toxic, better-tolerated therapies and then proceed to the more toxic chemotherapies.

The Magnitude of Clinical Benefit Scale

ESMO recently published an article describing a validated and reproducible tool that measures the magnitude of clinical benefit that can be expected from various therapies for solid tumors.[10] The scale can be applied to comparative studies evaluating the relative benefit of treatments using outcomes such as survival, quality of life, and toxicity. Upcoming ESMO guidelines will highlight the therapies that obtain the highest scores.

Interestingly, radium-223 is the only treatment for prostate cancer to receive the maximum score of 5. Docetaxel and cabazitaxel received scores of 3 and 2, respectively, perhaps based on their less favorable safety profiles.[6,7] A score of 4 was given to abiraterone and the enzalutamide data from the AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) trial.[3,4] Data from the PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) trial of enzalutamide received a score of 3.[5] The high score for radium-223 may be attributable to data from the ALSYMPCA trial showing not only improved survival but also improved time to symptomatic skeletal events, better quality of life, and reduced need for hospitalization.[1]

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