Imaging and Treatment Recommendations in Patients With Castrate-resistant Prostate Cancer

David M. Albala, MD
Associated Medical Professionals, Syracuse, NY

[Rev Urol. 2017;19(3):200–202 doi: 10.3909/riu193PracticeProfile]

Castrate-resistant prostate cancer (CRPC) is a form of advanced prostate cancer that is resistant to medical or surgical treatments to lower testosterone, and has spread to other parts of the body. Over 80% of men with CRPC (M0) will progress to metastatic castrate-resistant prostate cancer (mCRPC), with progression being quite rapid in over half of patients. A great deal of controversy exists on how these patients should be studied and treated. Prognosis is associated with several key factors, including the presence of bone pain, extent of disease on bone scan, and performance status. Bone metastases will occur in 90% of men with CRPC and can produce significant morbidity including pain, pathological fractures, spinal cord compression, and bone marrow failure. CRPC represents a spectrum of disease ranging from patients without metastasis or symptoms with rising prostate-specific antigen (PSA) levels despite androgen deprivation therapy to patients with metastasis and significant debilitation due to cancer symptoms.

Recent therapeutic advances have shown a significant survival advantage with monotherapy in trials with mCRPC patients. Optimal use of chemotherapy, second-generation androgen pathway inhibitors, immunotherapy, and targeted alpha therapy to achieve maximum clinical benefit has not been established. There are very few head-to-head studies that exist in the literature, and, as such, treatment decisions are based on limited nonrandomized comparisons. In addition, consideration of safety and tolerability are extremely important in choosing final treatments for this group of patients. The Prostate Cancer Radiographic Assessment for Detection of Advanced Recurrence Working Group (Radar 1 Group) is composed of medical oncologists, radiation oncologists, urologists, and nuclear medicine specialists, and tasked to provide recommendations for early identification of metastases in patients with prostate cancer. One of the key objectives of the working group was to provide a consensus regarding sequencing, combination, and "therapeutic layering" (the clinical point where one or more agents is added onto an existing therapy).

Currently, mCRPC is incurable. The goal of treatment is to extend life and provide the best quality of life for patients for as long as possible. Six agents have achieved US Food and Drug Administration approval. These agents can prolong survival. Current treatment guidelines include sipuleucel-T, docetaxel, abiraterone acetate, enzalutamide, carbazitaxel, and radium RA 223 dichloride. In addition to these agents, supportive treatments such as the bone-health modifiers denosumab and zolendronic

acid and external-beam radiation therapy (EBRT) are often used. Each of these agents is indicated for patients with M1 CRPC.

The results of the recommendations are described below.

Imaging Recommendations

The RADAR group suggested that imaging should be initiated when considering starting therapy for patients with CRPC, when therapies are changed to establish a new baseline, and after treatment has been completed to monitor disease progression. They cautioned against overutilization of imaging in clinical practice. The discordance between the response with PSA and radiographic imaging has created confusion in identifying disease progression. The group has recommended that imaging be performed when clinical or consistent and convincing biochemical progression is identified. The RADAR Group has recognized that radiolabeled choline positron emission tomography (PET-CT) was found to be more sensitive than conventional imaging (ultrasound, CT scan of the abdomen/pelvis, and bone scans) in selective patients with biochemical recurrence.

Current guidelines dictate that the patient should be screened early and often using the best available tools to identify potential metastasis and optimize treatment outcomes for patients with metastatic disease. For optimal effectiveness, the following factors should be taken into consideration when deciding on the frequency of imaging: individual risks, age, PSA doubling time (PSADT), Gleason grade, and overall patient health. Scans should be performed more frequently when the PSADT is less than 8 months. For patients with non-metastatic CRPC, the RADAR Guidelines recommend obtaining the first scan when the PSA level reaches 2 ng/mL. Imaging modalities recommended for the initial testing include 99 mTc-MDP scintigraphy and abdomen/pelvis/chest CT. If the imaging is negative, this should be followed by another scan when the PSA level reaches 5 ng/mL, and for every doubling of PSA level thereafter. Delays in ordering bone scans are common in clinical practice, resulting in delayed diagnosis of metastasis and delayed therapy, which can negatively impact patient outcomes.

Given the issues of sensitivity and specificity with traditional bone scans, newer options have been developed that may offer increased diagnostic accuracy in patients with mCRPC. These include 18F-sodium fluoride PET-CT, MRI, and CT scans. In an analysis of 10 studies, 18F-sodium fluoride PET scans were associated with pooled sensitivity and specificity of 96% and 98%, respectively. Other emerging scanning options include PET with choline tracers, targeted prostate-specific membrane antigen (PSMA), and whole-body MRI.

Treatment Recommendations

To date, no study of secondary hormone treatment has demonstrated any benefit in terms of survival. For patients who progress on androgen depletion therapy (ADT) without evidence of distant metastases, it is suggested that patients be screened for bone metastases and to monitor them for visceral metastases with abdomen and chest imaging. Because the androgen receptor remains active in most patients who have developed castrate-resistant disease, it is recommended by the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and other groups that ADT should be continued.

Currently, only patients with CRPC who have detectable macroscopic metastatic disease should be considered for systemic chemotherapy outside of the clinical trial. These patients should be referred early for possible chemotherapy, and should receive multidisciplinary care to maximize survival and quality of life. Docetaxel is a taxane drug that has proven effective in patients with CRPC. It had considered the standard of care for men with CRPC with detectable metastatic disease. These patients should receive 5 mg of prednisone bid. Several studies have shown that docetaxel improved survival compared with mitoxantrone/prednisone (median survival, 18.9 months vs 16.5 months). Clinical studies have suggested that treatment with docetaxel, 75 mg/m^2, administered intravenously every 3 weeks with 5 mg of oral prednisone twice daily should be offered to improve survival, disease control, symptom palliation, and quality of life. Chemotherapy should be initiated early in hormonally naive, newly diagnosed metastatic prostate cancer patients with high-volume disease, although recent reports of abiraterone in this setting appear to be promising. In low-volume disease, chemotherapy has not shown to be beneficial in these patients. For mCRPC, chemotherapy is generally not recommended initially. Therefore, to maintain a good quality of life, it may be logical to reserve chemotherapy for more symptomatic patients with metastatic prostate cancer, where survival benefit may be coupled with an additional pain palliative benefit.

Immunotherapy with sipuleucel-T should be considered first-line therapy for patients with mCRPC who are asymptomatic, have low

disease burden, and exhibit indolent disease characteristics. Sipuleucel-T, an autologous T cell–based immunotherapy, was shown to prolong survival (22% reduction in risk of death; HR, 0.78 [95% CI, 0.61-0.98; $P = .03$) in a key phase 3 trial (NCT0065442). Although sipuleucel-T prolonged median survival, it had no effect on number of bone metastases. Studies have shown that patients should receive this medication early in their disease. Sipuleucel-T should be considered for all newly diagnosed asymptomatic or minimally symptomatic mCRPC patients with low tumor burden. The duration of therapy is fixed with three doses and can be completed in five weeks.

Second-generation androgen pathway inhibitors (abiraterone and enzalutamide) should be considered following immunotherapy in the setting of biochemical or clinical progression. The FDA approved abiraterone acetate (the prodrug abiraterone and inhibitor of CYP17A1 that blocks extragonadal testicular, and intratumoral androgen synthesis) and enzalutamide (a direct inhibitor of the androgen receptor that attenuates its activation and signaling within the nucleus) in 2011 and 2012, respectively. These drugs can be initiated upon consecutive PSA rises. Early initiation philosophically is associated with a greater benefit, and these drugs should be considered to patients both who have taken sipuleucel-T treatment or those that may have a hard time getting sipuleulcel-T. Consecutive rises in PSA levels may indicate resistance.

Radium Ra 223 dichloride should be considered for patients with bone metastases on the emergence of signs and symptoms of impaired mobility, fatigue, or bone pain. Radium Ra 223 dichloride is an alpha-emitting radionuclide, approved for the treatment with mCRPC with symptomatic bone metastasis and no known visceral metastasis. Radium Ra 223 dichloride has an excellent safety profile with low risk for adverse effects on hematopoiesis, and has been recommended to be added to androgen pathway inhibitors in patients with bone metastasis and symptoms. The concurrent administration of radium Ra 223 dichloride and second-generation androgen pathway inhibitors appears to be well tolerated with similar toxicities compared with standard administration of radium Ra 223 dichloride alone.

There have been great strides in the management of mCRPC in the past few years. There is, however, a challenging task of selecting a treatment approach that will optimize patient outcomes. These selections must often be made without the results of large-scale, randomized, controlled clinical trials evaluating combination, sequential, and direct comparative protocols. ■

Bibliography

1. Crawford ED, Petrylak D, Shore N, et al S. The role of therapeutic layering in optimizing treatment for patients with castration-resistant prostate cancer. *Urology*. 2017;104:150159.
2. Armstrong AJ, Saad F, Phung D, et al. Clinical outcomes and survival surrogacy studies of prostate-specific antigen declines following enzalutamide in men with metastatic castration-resistant prostate cancer previously treated with docetaxel. *Cancer*. 2017;123:2303-2311.
3. El-Amm J, Aragon-Ching JB. The changing landscape in the treatment of metastatic castration-resistant prostate cancer. *Ther Adv Med Oncol*. 2013;5:25-40.
4. Kantoff PW, Higano CS, Shore ND, et al. (2010). Sipuleucel-T Immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.
5. Lorente D, Mateo J, Perez-Lopez R, et al. (2015). Sequencing of agents in castration-resistant prostate cancer. *Lancet Oncol*. 2015;16:e279-e292.
6. Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol*. 2015;16:509-521.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Prostate Cancer. Version 2.2017.
8. Parker C, Nilsson S, Heinrich D, et al. "Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer." *N Engl J Med*. 2013;369:213-223.
9. Saad F, Carles J, Gillessen S, et al. Radium-223 in an international early access program (EAP): effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients. *J Clin Oncol*. 2015;33(15 suppl): 5034-5034.