Advanced Prostate Cancer: Considerations for Advanced Practitioners

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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Abstract

At JADPRO Live Virtual 2020, Brenda Martone, MSN, ANP-BC, AOCNP®, discussed treatment options available for advanced prostate cancer patients and the role of genetics and genomics in patients with advanced prostate cancer.

With the introduction of novel agents for the treatment of advanced prostate cancer, the range of options with notable benefits has widened. The armamentarium now includes second-generation androgen receptor–targeting agents and several chemotherapeutics as well as new drugs targeting other oncogenic and genomic pathways. At the same time, the optimal choice for a given patient is often nuanced, as is the most effective sequential use of these agents. Advanced practitioners navigate patients through the maze of options, helping them make informed decisions and monitoring and managing their side effects. They are integral in assuring that patients derive the most possible benefit from advanced prostate cancer treatment.

At JADPRO Live Virtual 2020, Brenda Martone, MSN, ANP-BC, AOCNP®, of Northwestern Medicine, described current therapeutics and the factors that distinguish them.

UNDERSTANDING THE DEFINITIONS

Advanced prostate cancer is classified as hormone-naive metastatic disease or castration-resistant disease that is either nonmetastatic or metastatic. Men with advanced hormone-naive metastatic prostate cancer present with *de novo* metastases; they are not on androgen deprivation therapy (ADT) but may have been treated with ADT as neoadjuvant or adjuvant therapy concurrently with radiotherapy. Men whose disease is castration resistant are receiving ADT but have rising levels of prostate-specific antigen (PSA) despite continued suppression of testosterone.

Ms. Martone emphasized the need to offer all advanced prostate

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cancer patients genetic testing and genomic profiling to detect mutations that facilitate tumor growth. Testing can identify targeted treatment options, help determine the potential benefit of a platinum agent, guide treatment sequencing, and guide selection of patients for clinical trials. The finding of a germline mutation also triggers cascade testing of family members potentially at risk.

Beyond germline testing, somatic testing is also critical to look for relevant mutations, including *BRCA1/2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12* in the tumor itself. Tumors should also be tested for microsatellite instability (MSI-I)/mismatch repair deficiency (dMMR), which identifies candidates for pembrolizumab (Keytruda).

METASTATIC CASTRATION-NAIVE PROSTATE CANCER: CHANGING LANDSCAPE

Metastatic castration-naive prostate cancer (also referred to as hormone-sensitive cancer) has become very treatable. "Since 2014, this space basically has exploded with additional agents that not only treat the prostate cancer, but are all associated with an overall survival benefit," Ms. Martone said.

Because of the endocrine responsiveness of this malignancy, ADT remains the backbone of therapy, but androgen suppression alone is not enough. Add-on agents now making a difference in outcomes are the three second-generation androgen receptor inhibitors—abiraterone (Zytiga), enzalutamide (Xtandi), apalutamide (Erleada)—and the chemotherapeutic docetaxel, all of which are Category 1 recommendations from the National Comprehensive Cancer Network (NCCN). There is also a role for external beam radiation therapy to the primary tumor in men with low-volume disease.

The side effects of these agents are largely overlapping, although some are unique to a particular drug. Abiraterone's most common side effects include hypertension, lower extremity edema, fatigue, electrolyte imbalance, liver function abnormalities, and gastrointestinal distress. Clinicians should monitor for mineralocorticoid excess and closely monitor patients with cardiovascular disease (check magnesium, phosphorous, and potassium). They should also be vigilant for adrenal corticoid insufficiency and, if necessary, increase the dose of corticosteroids.

Enzalutamide can produce side effects of the central nervous system (CNS); therefore, patients with a history of seizures and perhaps other CNS issues are not good candidates. Common symptoms are fatigue, arthralgias, hypertension, nausea, diarrhea, generalized weakness, and dizziness. "In my clinical practice, I see the most profound fatigue with enzalutamide as compared to abiraterone or apalutamide," she said.

Apalutamide is associated with ischemic cardiovascular events; therefore, significant heart disease at baseline may be a contraindication. Increased risks of falls, fractures, and seizures have also been reported, as well as fatigue and arthralgias and, unlike with the other agents, rash and hypothyroidism, she said.

Docetaxel's typical side effects are neutropenia, fatigue, gastrointestinal distress, peripheral neuropathy, partial hair loss, and mucositis. There remains some debate as to the appropriate population for this drug. An overall survival benefit was shown in men with high-volume disease (Sweeney et al., 2015), which is defined as visceral metastases (lung, liver) or the presence of ≥ 4 bone lesions, one being outside the vertebral bodies and the pelvis, she said.

"The addition of docetaxel to ADT in men with high-volume disease, therefore, is basically the treatment of choice if they are fit for chemotherapy. Data remain controversial for its use in men with low-volume metastatic disease, meaning any disease that is not 'high volume,' " she said. Data on this population are awaited. Meanwhile, in the pivotal CHAARTED (Kyriakopoulos et al., 2018) and STAMPEDE trials (Parker et al., 2018), there was no survival benefit, "only additional toxicities" in men with low-volume disease, she indicated.

HOW TO CHOOSE AMONG THESE DRUGS?

Several factors can help narrow the choice of agent among these four preferred regimens: the patient's fitness for chemotherapy, volume of disease, performance status and functionality, comorbidities, medical and drug history, risk for falls, symptom load, need for a prompt response, number of metastatic sites, and, perhaps most importantly, patient preference.

"In my clinical practice, it's basically 50/50 in terms of who wants chemotherapy and who chooses an oral agent," she said. Docetaxel is given for 6 cycles and treatment is completed, while oral medications are taken daily until disease progression. "Also, these second-generation AR inhibitors are very expensive. Insurance, formularies, and copays sometimes dictate which agents we can use."

Advanced practitioners have an integral role in mutual decision-making: presenting the most appropriate options, helping patients understand them, and understanding the patient's own preferences and expectations. "If their expectation is not realistic, we can help them adjust those expectations so that they choose treatments appropriately," she commented.

RADIOTHERAPY TO THE PRIMARY IN CASTRATION-NAIVE METASTATIC DISEASE

Data are emerging in support of radiotherapy to the primary tumor in newly diagnosed metastatic prostate cancer. In STAMPEDE, the addition of radiotherapy to ADT and docetaxel reduced 3-year mortality by 32% (p = .007) in men with low-volume disease (but not high-volume disease), without increasing toxicity (Parker et al., 2018). The 3-year survival rates were 81% with radiotherapy vs. 73% with the standard of care alone. In the HORRAD trial, median time to PSA progression was extended for patients receiving radiotherapy vs. ADT alone (hazard ratio [HR], 0.78; p = .02; Boevé et al., 2019). Based on "impressive" differences in overall and failure-free survival, radiotherapy to the primary tumor is now the standard of care, she indicated.

The results are less clear for adding radiotherapy to a regimen of ADT and a second-generation androgen receptor inhibitor; however, it is not unreasonable to discuss this with patients who are not fit for, or do not want, chemotherapy, she said. Providers are encouraged to enroll patients on trials of this approach.

NONMETASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Men with castration-resistant prostate cancer have suppressed testosterone but a rising PSA while on ADT. They can present either in the metastatic or nonmetastatic setting. For the nonmetastatic patient, NCCN guidelines stratify patients by PSA doubling time, which is the time it takes in months for PSA levels to double. A doubling time < 10 months indicates a more aggressive cancer and an increased risk of metastases.

The treatment recommendations in this setting include the androgen receptor inhibitors apalutamide, darolutamide (Nubeqa), and enzalutamide (all with Category 1 recommendations), which have all been shown to significantly improve overall survival. Ms. Martone described the side effect profiles for these agents.

Darolutamide was found in the ARAMIS study to have a favorable safety profile, with no significant increase in adverse events or drug-drug interactions seen (Fizazi et al., 2019). Some patients, however, may experience fatigue, extremity pain, rash, reduced neutrophil count, increased liver enzymes, and increased bilirubin levels.

Enzalutamide's safety profile was previously described, but Ms. Martone emphasized "keeping an eye on patients' chemistries and blood counts, strength and balance, and cognitive changes and to watch for liver abnormalities... For balance, just ask patients to do the get up and go test, to walk in the hallway...Ask if they are having trouble focusing... Always assess for fatigue," she advised.

Apalutamide also carries a risk for falling, as she described earlier, and has some unique side effects not typically seen with other androgen receptor inhibitors. Clinicians should monitor for rash, hypothyroidism, and blood chemistries, especially for elevation of liver enzymes. Treatment for the macular maculopapular rash is symptomatic, using emollients, antihistamines, and topical corticosteroids if pruritic, or holding the medication if the rash is not well controlled.

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Recent developments in metastatic castration-resistant prostate cancer have resulted in multiple options for first- and second-line treatment (Figure 1).

Clinical factors that guide treatment choice include prior treatments (an agent with a novel mechanism of action is preferred), availability of

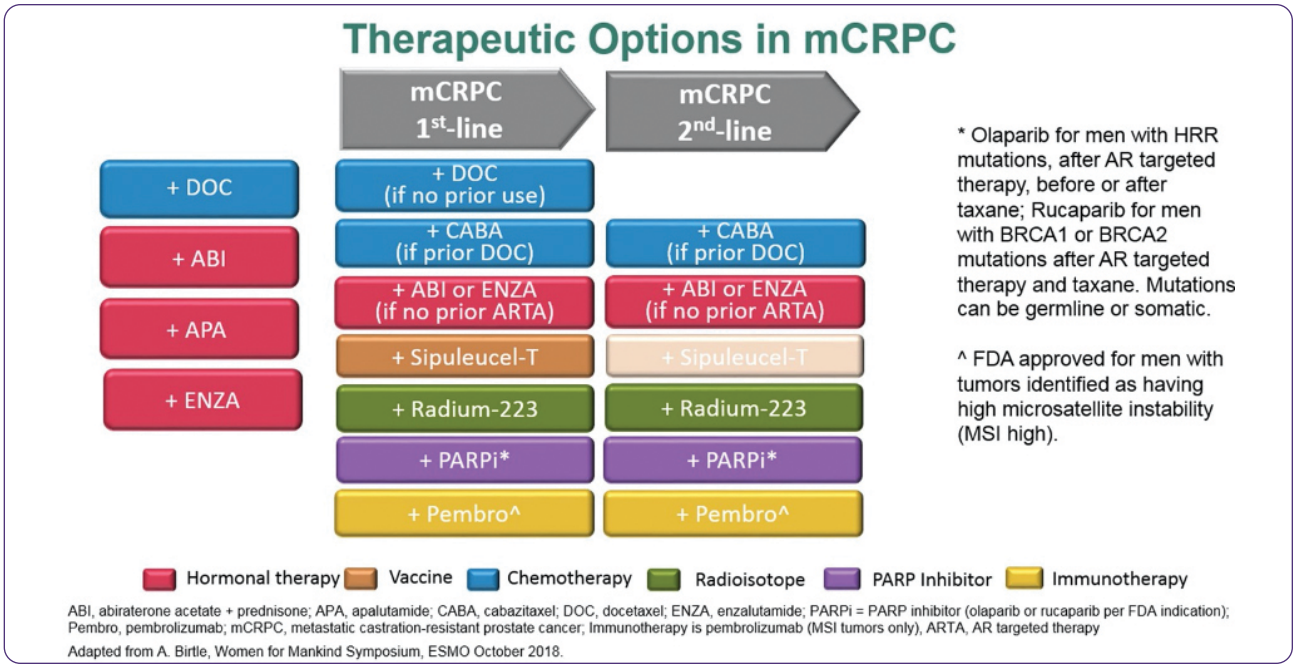

Figure 1. Therapeutic options in metastatic castration-resistant prostate cancer.

the chosen option, fitness for chemotherapy, presence of targetable mutations or microsatellite instability, and eligibility for a clinical trial.

Cabazitaxel (Jevtana), a taxane, is approved in this setting for patients previously treated with docetaxel, either in the castration-sensitive frontline metastatic setting or in castration-resistant disease. Side effects can include neutropenia, diarrhea, fatigue, nausea, vomiting, anemia, thrombocytopenia, sepsis, and renal failure.

Cabazitaxel joins abiraterone and enzalutamide in showing a survival benefit in patients. In the CARD trial, cabazitaxel proved superior in multiple outcomes vs. abiraterone and enzalutamide (de Wit et al., 2019). Median overall survival was 13.6 months with cabazitaxel and 11.0 months with the androgen signaling–targeted inhibitors (HR, 0.64; p = .008); imaging-based progression-free survival was also improved (HR, 0.54; p < .001). The CARD trial concluded that androgen receptor–targeting agents used sequentially were inferior to cabazitaxel in patients progressing after both docetaxel and either abiraterone or enzalutamide.

PARP INHIBITORS IN METASTATIC CASTRATION-RESISTANT DISEASE

BRCA genes, mutations of which occur in about 12% of prostate tumors, act as tumor suppressors in prostate cancer and play a pivotal role in cells' response to damage. The PROfound trial led to the approval of the first inhibitor of poly(ADP) ribose polymerase (PARP), after olaparib (Lynparza) significantly improved progression-free survival and radiographic progression-free survival compared with physician's choice of treatment (HR, 0.34; p < .0002; de Bono et al., 2020). The approval of rucaparib (Rubraca) has since followed, based on the TRITON2 trial in which 56% of patients responded to the PARP inhibitor and median duration of response was not reached (Abida et al., 2020).

While their safety profiles are similar, the approved indications of the two PARP inhibitors are slightly different. Olaparib is indicated for patients with deleterious or suspected deleterious germline or somatic homologous recombination repair genes who have progressed following treatment with enzalutamide or abiraterone. Rucaparib is indicated for men with deleterious *BRCA* mutations (germline and/or somatic) who have been treated with ADT and a taxane. The side effects include fatigue, asthenia, nausea, vomiting, anemia, and thrombocytopenia. With rucaparib, there have also been reports of elevated liver enzymes as well as diarrhea, constipation, and rash.

PEMBROLIZUMAB FOR MSI-H TUMORS

Pembrolizumab is the first checkpoint inhibitor approved in prostate cancer and is restricted to patients whose tumors are MSI-H/dMMR or carry a tumor mutational burden of 10 or higher. In KEYNOTE-199, which led to its approval, adverse events were reported in more than 60% of patients, especially fatigue, diarrhea, and decreased appetite (Antonarakis et al., 2020). Grade ≥ 3 toxicities were mostly colitis and fatigue, and immune-related events were seen in 16%, mostly colitis, hyperthyroidism, hypothyroidism, pneumonitis, and severe skin reactions.

ROLE OF BONE-TARGETED AGENTS

All men with metastatic castration-resistant prostate cancer should be taking calcium and vitamin D, and ideally a bone-strengthening agent that facilitates bone remodeling, either zoledronic acid or denosumab. The biggest concern with these drugs is osteonecrosis of the jaw; therefore, dental evaluation is important, with necessary interventions accomplished prior to starting on these drugs.

STAY TUNED

"Stay tuned! There's a lot happening in metastatic prostate cancer, including new agents in clinical trials. We are looking at optimal sequencing of therapies and combination therapies, which may give additional benefits," Ms. Martone said. "We continue to explore the impact of genetics and genomics and to identify new targeted agents."

"Prostate cancer treatment is not a race, it's a marathon. This means you want to maximize the total amount of benefit that you can get from treatments, and to make sure that your recommendation for a treatment change is not just based on a rising PSA, but on objective findings such as new lesions on bone scans or computed tomography that indicate a change is needed," she added. ●

Disclosure

Ms. Martone had no conflicts of interest to disclose.

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