Therapeutic Advances in Prostate Cancer

PRESENTED BY ROBERT DREICER, MD, MS, MACP, FASCO, and MORGANE C. DIVEN, PharmD, BCOP

From University of Virginia, Charlottesville, Virginia; and Phoenix VA Health Care System, Phoenix, Arizona

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With seven different agents approved by the FDA for the treatment of advanced prostate cancer since 2004, and new evidence for integrating some of these agents earlier in the disease, clinicians are increasingly challenged with determining the optimal sequencing of these agents. At JADPRO Live 2018, Robert Dreicer, MD, MS, MACP, FASCO, of the University of Virginia, discussed the clinical data of emerging and current agents for the treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC) and evaluated the role of docetaxel and abiraterone in newly diagnosed metastatic prostate cancer. Dr. Dreicer also interpreted emerging data regarding the role of genomics in metastatic castration-sensitive and -resistant prostate cancer. Morgane C. Diven, PharmD, BCOP, of the Phoenix VA Health Care System shared strategies to manage toxicities of current and emerging treatments for advanced prostate cancer.

MANAGING PATIENTS WITH PSA-ONLY DISEASE

As Dr. Dreicer explained, approximately 30% or more of patients who have undergone curative-intent surgery or radiotherapy will have a detectible PSA post therapy. However, most patients who have a detectible PSA after definitive local therapy do not die of prostate cancer, said Dr. Dreicer, so therein lies one of the dilemmas about managing the disease.

"There is limited prospective data to suggest that most patients treated with androgen deprivation therapy (ADT) benefit from early treatment, i.e., in the nonmetastatic setting. PSA response will occur; however, many of these patients will have disease that evolves to nonmetastatic, castration-resistant, PSA-only disease.

Castration-resistant PSA-only disease is defined as a testosterone level less than 50 ng/dL, rising PSA, and no overt evidence of metastatic disease on standard imaging. The relationship between a shortening PSA doubling time and risk for disease progression has been demonstrated in prospective studies. When PSA doubling time drops below 8 months, there is a much higher incidence of the development of radiographic evidence of metastatic disease.

At the 2018 American Society of Clinical Oncology (ASCO) Geni-

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tourinary Cancers Symposium, two large, phase III trials showed significant differences in metastasis-free survival with second-generation androgen receptor (AR) antagonists vs. placebo in patients with castration-resistant nonmetastatic disease and a PSA doubling time of less than 10 months (Hussain et al., 2018; Smith et al., 2018). Both apalutamide (Erleada) and enzalutamide (Xtandi) led to 2 years of median improvement in metastasis-free survival, which are "grand-slam kind of differences," said Dr. Dreicer, and the hazard ratios indicate a greater than 70% reduction of metastatic disease.

Based on recent data, another AR antagonist, darolutamide, may soon be approved as well, Dr. Dreicer added. However, none of these drugs have been directly compared to each other.

METASTATIC PROSTATE CANCER

Whether or not it can be attributed to changes in screening in the United States, rates of hormone-sensitive metastatic prostate cancer have dropped significantly over the past 4 decades, but ADT has remained the standard of care for 80 years. According to Dr. Dreicer, recent evidence has shown that once a patient starts on ADT, their PSA nadir is predictive of survival.

The CHAARTED trial, conducted in patients considered to have either high-volume or low-volume metastatic disease, showed that patients randomized to ADT plus 6 cycles of docetaxel had a survival benefit of more than 1 year vs. ADT alone (Sweeney et al., 2014). However, not all patients are appropriate candidates for docetaxel. In high-volume disease, said Dr. Dreicer, survival advantage has been maintained with longer follow-up, but patients with low-volume disease do not benefit. Following the publication of the CHAARTED study, the addition of docetaxel for many patients with hormone-sensitive metastatic disease became a standard of care.

A lyase inhibitor called abiraterone acetate (Zytiga), which has been approved for castration-sensitive metastatic prostate cancer on the basis of two survival studies, was similarly studied in hormone-sensitive metastatic prostate cancer. In the LATITUDE study, said Dr. Dreicer, patients randomized to ADT plus abiraterone plus prednisone showed a "striking survival benefit" vs. ADT alone (Fizazi et al., 2017). A study called STAMPEDE, which enrolled patients not only with metastatic disease but locally advanced or node-positive disease, also showed a survival benefit (James et al., 2017).

Following the publication of both of these studies, clinicians are left with two options to improve survival in patients with metastatic prostate cancer being treated with ADT: the addition of docetaxel or abiraterone. Unfortunately, said Dr. Dreicer, there are no comparative data.

"Clinicians must make a choice, discuss it with their patient, and press on," he said. "Both docetaxel and abiraterone have striking level 1 evidence to support their use in patients with high-volume and poor-risk disease."

While low-volume patients do not benefit from docetaxel, the data are less clear regarding low-volume patients and abiraterone, he added.

GERMLINE MUTATION TESTING

Finally, an area that is rapidly evolving is the genomics of prostate cancer. As Dr. Dreicer explained, important mutations in prostate cancer can be both germline (inherited) or somatic (occurring after conception).

"Identifying germline mutations is important for patients because they speak to family risk and impact treatment choices over time," said Dr. Dreicer, who noted that 8% to 12% of patients harbor germline homologous recombination repair mutations. "I've begun to do germline testing in almost all patients with de novo metastatic disease to not only define their risk but their family's, as well."

Somatic mutations, on the other hand, are present in approximately 25% of patients with castration-resistant, metastatic prostate cancer. The most common of these homologous recombinant repair mutations are *BRCA1*, *BRCA2*, and *ATM,* and they represent between 10% to 15% of castration-resistant metastatic patients. A study published in *The New England Journal of Medicine* demonstrated that patients who had homologous recombination repair mutations (many of these patients were heavily treated with other therapies) had a very significant response to the drug olaparib (Lynparza), one of the PARP inhibitors targeted against *BRCA* (Mateo et al., 2015).

"Because PARP basically inhibits the ability for these double-strand DNA breaks to be repaired, PARP inhibitors may have more activity in prostate cancer where platinum therapy is not routinely used, although platinum may have viable utility in patients who express this type of mutation," said Dr. Dreicer, who noted that there are multiple ongoing trials of different PARP inhibitors in this space. "It would not surprise me if within 12 to 18 months, one or two or three agents will be approved."

"Once PARPs are approved in prostate cancer, clinicians are going to start testing somatically because they will probably not be able to administer this drug without demonstrating the mutation," he added.

Finally, although prostate cancer compared to lung cancer or urothelial cancer has a lower mutational burden, patients who express microsatellite instability (MSI)–high prostate cancer (approximately 2% to 3% of patients) have the ability to receive the immunotherapy drug pembrolizumab (Keytruda). MSI-high testing is increasingly being considered, said Dr. Dreicer, because of the potential to use the checkpoint inhibitor, but the incidence is relatively small (Lemery, Keegan, & Pazdur, 2017).

MANAGEMENT OF TOXICITIES

As Dr. Diven explained, clinicians are used to managing or evaluating many of the toxicities associated with prostate cancer therapies, but it is important to consider the patient when choosing between available oral agents.

"When patients are receiving intravenous agents, they're being seen regularly," said Dr. Diven. "With oral oncolytics, however, patients may not receive the same attention."

In order to appropriately monitor patients for adverse drug events, Dr. Diven and colleagues have worked hard to ensure patients receiving oral oncolytics utilize dietitians, social workers, pharmacists, and nurses.

"I always remind patients to take advantage of all the support that we make available for them to help them receive the care they need, and that includes the support of primary care and specialists," Dr. Diven added.

Nevertheless, Dr. Diven emphasized that current agents for prostate cancer are generally well tolerated with manageable toxicities.

Disclosure

Dr. Dreicer has acted as a consultant for Astellas, AstraZeneca, Genentech/Roche, Incyte, and Pfizer. Dr. Diven has no conflicts of interest to disclose.

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