New Treatment Options in Castration-Resistant Prostate Cancer

Presented by Andrew J. Armstrong, MD, ScM

Abstract
Most of the updates in the 2015 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer center on the systemic therapy front, with a host of newer agents in the mix. At the NCCN 20th Annual Conference, Dr. Andrew J. Armstrong discussed some of the key developments in metastatic castration-resistant and castration-sensitive prostate cancer, particularly the conflicting results on repurposing docetaxel in castration-sensitive disease, the specific population who may experience greater survival benefit from immunotherapy in castration-resistant disease, updated data on the use of androgen receptor and biosynthesis inhibitors, and the emerging role of AR-V7 (androgen-receptor splice variant 7 messenger RNA) as a biomarker of treatment response. (J Natl Compr Canc Netw 2015;13:690–693)

The prostate cancer disease state model has evolved over the past several years as new therapeutic options have emerged, so we are now facing multiple lines of effective systemic therapies for this disease,” announced Andrew J. Armstrong, MD, ScM, Associate Professor of Medicine, Co-Director of Clinical Research Program at Duke Cancer Institute, and a member of the NCCN Guidelines Panel for Prostate Cancer. However, “the appropriate sequence of these agents is not well-known,” he admitted, and potential castration-resistant prostate cancer (CRPC) biomarkers may help to guide therapeutic choices for these patients in the not-too-distant future.

Although many men present with metastatic prostate cancer, most progress through local disease, rising prostate-specific antigen (PSA) levels and local therapy, and then to nonmetastatic CRPC (Figure 1). They move through first, second, and third lines of therapies, often sequencing through secondary hormonal strategies such as androgens (eg, enzalutamide), androgen synthesis inhibitors (eg, abiraterone), immunotherapy (eg, sipuleucel-T), taxane-based chemotherapy, and radioisotopic therapy, such as the alpha emitter radium-223. In fact, they often face fourth-line options and beyond as their disease transitions to treatment-refractory metastatic CRPC. “This time period is often measured in many years to decades from the time of diagnosis,” noted Dr. Armstrong.

Mixed Clinical Trial Results With Early Docetaxel
Support for the use of docetaxel in metastatic castration-sensitive prostate cancer came from the long-standing phase III ECOG-led CHAARTED trial of nearly 800 patients.1 Compared with those given androgen-deprivation therapy (ADT) alone, patients who received ADT and docetaxel had a longer overall survival (OS; 57.6 vs 44.0 months), which was not only statistically significant but clinically relevant. “The hazard ratio [HR, 0.61] for survival was more impressive than any of the past HRs seen with any other therapies for CRPC,” revealed Dr. Armstrong.

Moreover, patients with high-volume metastatic disease (visceral metastases, ≥4 bone metastases, and at least on extra-axial metastasis) had a 17-month improvement in median OS. Dr. Armstrong mentioned 3 other benefits associated with the use of early docetaxel in these patients: better PSA response, longer time to CRPC, and longer time to clinical disease progression.

In contrast, results from the randomized phase III GETUG-AFU 15 trial did not show an improvement
in OS, even in men with high-volume or high-risk metastatic castration-specific disease, with the addition of docetaxel to ADT. In fact, the investigators concluded, “Docetaxel should not be used as part of first-line treatment for patients with noncastrated metastatic prostate cancer.”

Dr. Armstrong offered a possible explanation for the differing study results (Figure 2). “Perhaps poor-risk, high-volume patients have a different biology than low-risk, low-volume patients.” Or, he added, both groups of patients benefit equally, but the studies were underpowered in this good-risk subset, while the ECOG CHAARTED trial was the only one sufficiently powered with long term follow-up in the high-volume subset. “It will take a meta-analysis of these trials to know whether docetaxel should be routinely used in these lower-volume or lower-risk patients,” he concluded.

**Immunotherapy**

Currently, sipuleucel-T remains the only immunotherapeutic agent approved in CRPC. It was approved several years ago based on the results of the IMPACT study. Dr. Armstrong focused on the more recent finding from this clinical trial, which demonstrated a trend toward a greater survival benefit with sipuleucel-T in patients with a lower baseline PSA level. In those with a PSA level greater than 134.1 ng/mL (the worst prognostic subset), OS difference was only 2.8 months. However, in those with a PSA level less than 22.1 ng/mL, the difference in OS was 13.0 months.

“I would choose the patients with lower PSA levels and lower-risk metastatic CRPC disease for sipuleucel-T to maximize the benefits and minimize the risks,” stated Dr. Armstrong. Based on the IMPACT trial results, a case could be made for starting immunotherapy as an early treatment strategy in sequencing algorithms for men with asymptomatic to minimally symptomatic metastatic CRPC.

**Androgen Receptor and Biosynthesis Inhibitors**

New supporting data for the use of enzalutamide have emerged from the updated analyses of the PREVAIL trial. In more than 1700 men with chemotherapy-naive metastatic CRPC after docetaxel use, enzalutamide improved both OS and radiographic progression-free survival, with an 81% risk reduction in progression-free survival and a 29% reduction in the risk of death. “Improvement in progression-free survival was seen whether you had visceral disease to...”

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**Figure 1** Prostate cancer clinical states model. Abbreviations: CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.
the liver or lungs or nonvisceral disease, and this agent seemed to provide clinical benefit in all subsets of men that were evaluated,” explained Dr. Armstrong.

Fatigue, fall risk, and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment. In fact, hypertension occurred 2 to 3 times as often with enzalutamide, Dr. Armstrong noted. “There should be some vigilance to perform blood pressure monitoring [with enzalutamide], much like with abiraterone,” he emphasized. The risk of seizures was low at 0.1% in both groups, including placebo-treated men.

Updated data from the key pivotal trial of abiraterone were reported recently. In the final analysis of the phase III COU-AA-302 study, median OS was longer with abiraterone than placebo in chemotherapy-naïve men with metastatic CRPC (HR, 0.81). This 20% to 30% improvement in OS and the absolute survival of nearly 3 years was similar to that with enzalutamide and is a substantial improvement based on historic data, indicating that these men are living longer with greater access to effective systemic therapies, noted Dr. Armstrong.

Resistance mechanisms to enzalutamide and abiraterone have been studied. For example, detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from patients with CRPC may be associated with resistance to these 2 agents. In fact, AR-V7 may represent a potential biomarker of treatment response. Antounarakis et al discovered that patients who were AR-V7–negative responded better to enzalutamide and much better to abiraterone, whereas those who were AR-V7–positive did not respond to either drug. With this method, “you could predict...
and is typically offered to men following progression on one novel hormonal therapy, such as abiraterone or enzalutamide. Ongoing studies are evaluating the earlier use of this agent in combination with these novel hormonal therapies.

References


