New Developments in the Treatment of Castration-Resistant Prostate Cancer

Presented by Celestia S. Higano, MD

*Abstract*

During the past 4 years, a host of new agents have been approved for the treatment of patients with advanced prostate cancer. As a result, selecting the right agent for the right patient at the right time is a clinical challenge. At the NCCN 19th Annual Conference, Dr. Celestia Higano explored the rationale behind such therapeutic decisions and the supporting clinical trial data. She reviewed the different classes of therapeutic agents, from immunotherapy and hormonal therapies to chemotherapy and radioisotopes, and offered suggestions for the clinical scenarios in which they may be used most successfully. (J Natl Compr Canc Netw 2014;12:773–776)

Understanding clinical disease states in castration-resistant prostate cancer (CRPC) is important to making intelligent choices for therapy for patients, said Celestia S. Higano, MD, Professor, Departments of Medicine and Urology, University of Washington/Seattle Cancer Care Alliance, Seattle, and a member of the NCCN Guidelines Panel for Prostate Cancer. “Metastatic castration-resistant prostate cancer has become quite confusing, given all the changes that have happened during the last 4 years,” she added. When deciding which treatment is best for a patient in a given situation, it is necessary to consider the pace of the disease, presence or absence of symptoms, and presence of lung, liver, nodal, or other soft tissue disease.

*Immunotherapy: Early in the Disease Course*

Sipuleucel-T is a treatment option that is optimally used early in the course of metastatic CRPC, noted Dr. Higano, before numerous second-line therapies, including chemotherapy and corticosteroids, have been tried. Sipuleucel-T is indicated for asymptomatic or minimally symptomatic patients with a lower disease burden who have a robust immune system, she added, rather than those with rapidly progressing disease or liver metastases.

The supporting data behind the use of sipuleucel-T for advanced, asymptomatic CRPC center on 3 clinical trials that include 737 patients.1–3 In the IMPACT trial, Kantoff et al2 showed a 4.1 month improvement in median overall survival (OS; 25.8 vs 21.7 months) in those who received sipuleucel-T compared with placebo at a median follow up of 36.5 months. In the first 6 months, no survival difference was seen between the groups, but the survival curves separate after this time, showing benefit in terms of survival. “Immunotherapy does not kick in right away like we see with chemotherapy or hormonal therapy,” noted Dr. Higano. “It takes time to make a difference.”

The survival benefits with sipuleucel-T were consistently seen across all 3 trials.1–3 In addition, it may show a beneficial trend in delaying the time to disease-related pain and a potential advantage in terms of time to first opioid use with immunotherapy, she said.

Dr. Higano briefly discussed the importance of educating the patient and family about sipuleucel-T to re-
duce unrealistic expectations. The step-by-step process involved with immunotherapy infusions should be clearly explained to patients. “The therapy is over and done in 1 month,” she noted. Additionally, the patient and family should be informed that a decline in prostate-specific antigen (PSA) level is not expected with immunotherapy. Furthermore, as some patients may develop pain after infusion with sipuleucel-T, Dr. Higano encourages baseline imaging and monthly clinical evaluations for symptomatic disease progression and standard imaging at 3 months after sipuleucel-T administration. “This way we can reassure patients and ourselves that if things are stable, we can sit and watch. If not, we may want to move on to something different.”

**Newer Hormonal Therapies: Before and After Chemotherapy**

Abiraterone acetate and enzalutamide are newer hormonal agents that have been studied in the pre-docetaxel and post-docetaxel settings for metastatic CRPC (Table 1). According to the post-docetaxel phase III COU-AA-301 and AFFIRM trials, both agents significantly improved outcomes.

Of the nearly 1200 patients with metastatic CRPC who enrolled in the COU-AA-301 trial, those who received abiraterone acetate plus prednisone had a longer median OS than those who received prednisone and placebo (14.8 vs 10.9 months). Combination abiraterone acetate and prednisone offered benefits in terms of pain relief, delayed pain progression, and prevention of skeletal-related events. Importantly, Dr. Higano noted that prednisone itself is an active agent that may have had a role in the trial results.

Enzalutamide showed benefit over placebo in median OS (18.4 vs 13.6 months) in the AFFIRM trial. Furthermore, improved outcomes were shown in both younger (<75 years) and older patients.

Based on these data reports, Dr. Higano said, “both drugs showed a significant difference in median overall survival, with very favorable hazard ratios, and a delay in radiographic progression-free survival, but since these drugs were not compared head-to-head, one cannot conclude from the data that one drug is superior to the other.”

The benefits of both abiraterone acetate and enzalutamide were also seen in the pre-docetaxel phase III trials (COU-AA-302 and PREVAIL), although the difference in median OS in the COU-AA-302 study did not quite reach statistical significance. Again, the median radiographic progression-free survival was longer in the groups treated with the newer hormonal agents than in those who were not.

Dr. Higano predicted that enzalutamide will be soon be approved by the FDA in addition to abiraterone, which is already approved in the pre-docetaxel setting. “Things will change over time,” she added, “and likely most patients will be treated with abiraterone acetate and enzalutamide before chemotherapy.”

**Chemotherapy: Later in the Disease Course**

Many chemotherapeutic agents are used to treat metastatic CRPC, such as taxane combinations, mitoxantrone, and doxorubicin hydrochloride. “Some patients still experience long responses to mitoxantrone, which in the past was the only drug available that was shown to have palliative, if not an overall survival, benefit,” admitted Dr. Higano. However, only docetaxel and cabazitaxel offer a survival benefit, she added.

Although combination docetaxel and cabazitaxel offer a survival benefit, she added.
chemotherapy, it is usually reserved for symptomatic patients or those with rapidly progressing disease. "In my clinic, most patients with no symptoms do not want chemotherapy at this point, particularly when there are other, less-toxic agents," said Dr. Higano.

Supporting data for the use of cabazitaxel are shown in the TROPIC trial. This phase III study included 755 men with metastatic CRPC who had received previous hormone therapy but whose disease had progressed during or after treatment with a docetaxel-containing regimen. All patients were given oral prednisone and randomized to receive mitoxantrone or cabazitaxel. At the cut-off for final analysis, the median OS favored cabazitaxel (15.1 vs 12.7 months; hazard ratio [HR], 0.70).

Dr. Higano used the Kaplan-Meier survival curve for this trial to illustrate how to use these curves to calculate best and worst case scenarios to present to patients. For example, the 15.1 months median survival for cabazitaxel is representative of a typical patient, with extremes for lower- and upper-typical case scenarios closer to 9.4 and 25.0 months, respectively. Such ranges may be more meaningful than “median survival” times in patient discussions.

In terms of adverse events, more patients in the cabazitaxel group had a grade 3 or higher toxicity than those in the mitoxantrone group (57% vs 39%). The most common significant adverse events (≥ grade 3) for cabazitaxel were neutropenia and diarrhea.

"Because of the toxicity, some people have not been too enthused about using cabazitaxel," stated Dr. Higano. However, with the proper maneuvers, she believes it can be used safely. “In our clinic, we often start with a lower dose [20 mg/m²] and use growth factors in all patients.”

**Radium-223: For Symptomatic Metastatic Disease**

In May 2013, radium-223 was approved by the FDA for treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease. Radium-223 is an alpha-emitting agent that naturally targets new bone growth in and around bone metastases.

Supporting data for the use of radium-223 in metastatic prostate cancer came from the ALSYMPCA trial. In this phase III study, 921 patients with CRPC and bone metastases were randomized to receive 6 injections of radium-223 or placebo. According to an updated analysis, an OS benefit was seen with radium-223 over placebo (14.9 vs 11.3 months; HR, 0.70). In addition, the median time to first symptomatic skeletal event was longer with radium-223 than placebo (15.6 vs 9.8 months). Less benefit with radium-223 was seen in those with less than 6 metastases than in other subgroups. As a result, Dr. Higano suggested saving this treatment for later in the disease course for patients with more extensive metastatic disease.

Adverse events of interest with radium-223 included thrombocytopenia and diarrhea. Dr. Higano indicated that the diarrhea is likely related to intestinal elimination of radium-223 while the cytopenia may be exacerbated by intrinsic bone marrow involvement by tumor.

Practical considerations are necessary with radium-223, because it should only be given by those licensed to handle such isotopes, such as nuclear medicine physicians or radiation oncologists. Unlike beta- and gamma-emitting waves, alpha waves do not penetrate the skin, which "speaks to the relative lack of toxicity for people handling it or receiving it," added Dr. Higano. In addition, predosing checklists can help determine whether a patient meets the eligibility criteria for treatment with radium-223 (Figure 1).

Many unanswered questions remain regarding the use of radium-223 in metastatic prostate cancer, including the duration of pain control. However, the use of radium-223 in combination with docetaxel...
does not seem to be one of them. “Although radium-223 is nonmyelotoxic alone, when combined with docetaxel in a phase I trial, it showed unexpected hematologic toxicity, and so the combination is not recommended at the present time outside of a clinical trial,” concluded Dr. Higano.

References