Treatment sequencing in metastatic castrate-resistant prostate cancer

The treatment of metastatic castrate resistant prostate cancer (mCRPC) has been rapidly advancing. Years of research effort have culminated, in the approvals of five active agents that prolong patient survival. However, as a practicing clinician, I and others have observed that two-thirds of patients do not receive the full benefits of these new treatments, particularly chemotherapy. I suggest that the novel oral hormonal agents abiraterone (Zytiga, product of Janssen, a subsidiary of Johnson and Johnson) and enzalutamide (product of Astellas-Medivation) are over-utilized for patient treatment, while chemotherapy with docetaxel and cabazitaxel is somewhat under-utilized.

The reasons for this are numerous, but may boil down to the ease of treatment with the oral hormonal agents vs. the relative toxicity of chemotherapy. Nevertheless, while there are certainly differences in toxicity between the two drug classes, I contend that the under-utilization of chemotherapy, while at the same time continuing a patient whose disease is progressing on oral hormonal agents, is not in the best interest of that patient. But this pattern of treatment is precisely what is happening in practices throughout the country, with adverse impacts on patients' lives.

Increasing data in the literature describes cross-resistance between one oral hormonal drug (either abiraterone followed by enzalutamide or the reverse) and another. Two studies in the post-chemotherapy setting examined enzalutamide treatment followed by abiraterone. In a grand total of 68 patients, only 3% had a >50% decrease in PSA (prostate specific antigen, a bloodstream marker of disease activity). The median disease progression-free survival was only approximately 3 mo. Patients treated first with abiraterone and then with enzalutamide fared somewhat better. A >50% decline in the PSA was achieved in approximately 20% of the patients. Clinical researchers at Duke University also described their own experiences in both chemotherapy-naïve and chemotherapy-treated patients. Only 1 of 9 (11%) of the abiraterone-treated patients in each category responded with a PSA decline of >50% to subsequent enzalutamide treatment. Other studies also produced very modest responses when one oral agent was followed by another. Despite earlier hopes, abiraterone and enzalutamide appear to be cross-resistant, i.e., once a patient's prostate cancer becomes resistant to one of these drugs, he is also resistant to the other.

While treatment with one hormonal agent after another is common in the community, this practice often does not take into account the fact that chemotherapy is a viable treatment alternative for men with mCRPC. Fortunately, the chemotherapeutic agent cabazitaxel does not seem to be cross-resistant with the oral hormonal agents. A PSA decline of >50% was achieved in 28 of 79 (35%) in patients treated first with an oral-hormonal agent. In addition, pre-clinical data suggest that cabazitaxel may be killing cells by an mechanism that is independent of the androgen receptor. This is unlike abiraterone and enzalutamide; treatment of advanced prostate cancer patients with these agents induces a specific mutation in the androgen receptor that renders it insensitive to

these drugs.

While the use of docetaxel can be associated with high-grade fatigue, cabazitaxel is a well-tolerated drug, even in the over-80 population. The diarrhea observed in the initial trial has failed to materialize in the thousands of patients treated subsequently. Clinicians universally note the diminished fatigue and greater tolerability vs. docetaxel.

However, it is not likely that patients with poor performance status and large volumes of disease will respond to treatment. Therefore, as patients progress on therapy, all available treatment options must be considered. Treatments that are no longer active should be discontinued. Chemotherapy is a viable option for patients: Oft-underutilized cabazitaxel is an active and important part of the therapeutic armamentarium which when administered correctly, is safe, effective, and scientifically sensible.

CA Stein

City of Hope, Duarte, CA

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