Urol Colomb. 2016;25(3):198–200

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EDITORIAL

Castration-resistant prostate cancer: Why should urologists care?

Cáncer de próstata resistente a la castración: ¿por qué les debe importar a los urólogos?

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It seems like yesterday when I was sitting at the American Society of Clinical Oncology (ASCO) Program Committee section for Genitourinary oncology as part of a multi-disciplinary team of medical oncologists, urologists and radiation oncologists deciding what prostate cancer abstracts to consider for the annual meeting a few months later. At that time, we were so excited that finally two GU abstracts were making the ''big time'' as key showcased papers. I am referring to the seminal work of Eisenberger et al. and Petrylak and colleagues who were presenting overall survival benefit of Docetaxel in CRPC, which at that time was still called, ''Hormone refractory prostate cancer''.[1,2] While this might seem like ancient history, this was 2004! Thinking back to the excitement, I do not believe any of us imagined that a decade later we would have 6 more novel agents approved and in use for CRPC.[3] Truly, the time from 2004 to the present has been amazing for us and our patients with advanced prostate cancer! Urologists care for most men in the World with prostate cancer and we are with them when they transition from early to late stage and from hormone-sensitive to hormone refractory. We have the unique opportunity to guide early decisions regarding proper work-up and appropriate sequencing of new agents. We should and must maintain our skill set in this exciting area of our specialty.

Going back to Docetaxel, it is important to recognize that the modest yet significant and first-in-class survival benefit demonstrated by Petrylak, Eisenberger, Tannock and their colleagues, were not the end of the story. My colleagues did some very nice follow up work on risk-stratification and benefit to Docetaxel.[4–8] For the men who achieved a robust early PSA response and/or other risk-stratification, Armstrong and colleagues showed clinically significant survival improvements of Docetaxel. Furthering on improved risk-stratification, Halabi and associates also from my center, developed an updated prognostic model for CRPC and primary chemotherapy.[9] The key point here is that the novel agents being studied now to further survival must be

DOI of original article:
http://dx.doi.org/10.1016/j.uroco.2016.07.001
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http://dx.doi.org/10.1016/j.uroco.2016.07.002
0120-789X/

examined in a risk-stratified way and should be sequenced based on best current research. Finally, as urologists, we are very exciting about the striking improved survival for use of Docetaxel in newly diagnosed men with M1 hormone sensitive prostate cancer based on CHARTED and STAMPEDE trials.[10,11]

At our center, the most common novel agent sequencing for metastatic CRPC would be as follows: sipuleucel-T (Provenge®), Abiraterone (ZYTIGA®) or Enzalutamide (XTANDI®), Docetaxel or (TAXOTERE®) Radium-223 (Xofigo®), and cabazitaxel (Jevtana®) while maintaining primary androgen deprivation (LHRH/GnRH agents or orchiectomy). The American Urological Association (AUA) has done a very good job of educating urologists using their ''Index Patient'' approach.[12] Using six typical index case scenarios, clinicians are able to see examples of proper novel therapeutic sequencing.

Sipuleucel-T immunotherapy showed a 4.1 month median survival benefit for asymptomatic or minimally symptomatic metastatic CRPC patients in the pre chemotherapy setting.[13] Recently, the results of the pivotal phase III trial were stratified/risk assessed by starting PSA level showing that men with the lowest quartile of PSA (less than about 22 ng/ml when therapy was initiated) had a survival benefit of about one year.[14] This lowest PSA quartile data is the reason we prefer to sequence this agent early in the course of mCRPC and this group of patients is most commonly still under the care of urologists.

Next, the new oral hormonal agents, Abiraterone or Enzalutamide would most commonly be sequenced in. Both Abiraterone and enzaliutamide are FDA-approved for use before Docetaxel-based chemotherapy. Both agents will be expected to be effective for 15–17 months before clinical progression in the typical patient with mCRPC when the agents are used in a similar fashion to how they were used in their respective phase III trials.[15,16] However, once one agent becomes ineffective, the other agent is not generally able to deliver another 15–17 months of use and 3–6 months is a more typical short-lived response. Current research with the mutated androgen receptor, AR-V7, found in circulating tumor cells suggests that the presence of this novel biomarker predicts resistance to Abiraterone and Enzalutamide.[17] In the future, measuring this and other novel molecular biomarkers may better direct drug sequencing. For example, we would move directly to chemotherapy or another novel therapeutic for men who harbored AR-V7 rather than moving from Abiraterone to Enzalutamide or the reverse sequence.

Finally, the FDA-approved agent, Radium-223 (Xofigo®) is a novel radiopharmaceutical agent that not only can treat symptomatic bone metastases, but was associated with improved survival for men with mCRPC.[18] As an alpha particle agent, it does not have the bone marrow toxicity that was associated with radiopharmaceuticals used in advanced prostate cancer, such as strontium or samarium. The FDA-approved use of Radium-223 is for 6 monthly injections that can be ordered by a urologist and administered by a radiation oncologist or a nuclear medicine physician. It is important to sequence this agent while the patient is healthy enough to receive the full 6 cycles so he can hopefully have the survival benefit associated with the full treatment course.

In summary, the field of CRPC has expanded a lot since 2004 and urologists have an expanding knowledge base to tackle. While daunting, it is important for we as urologists to maintain our expertise in all prostate cancer disease states. Our patients will be better served when we are armed with this evolving menu of options.

Very respectfully,

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