Assessing the utility of cabazitaxel in mCRPC

Scott A. North, MD, FRCPC, MHPE

Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, AB, Canada

Cite as: *Can Urol Assoc J* 2016;10(3-4):111-2. http://dx.doi.org/10.5489/cuaj.3721

See related article on page 102.

Saad et al report on the utility of cabazitaxel in men with metastatic castration-resistant prostate cancer (mCRPC) who either did or did not receive prior abiraterone acetate in addition to docetaxel chemotherapy.[1] These results were generated as part of an international, expanded-access study, in which 61 Canadian men were enrolled and for whom prior abiraterone exposure was known for 60 subjects.

In recent years, the treatment landscape for mCRPC has changed dramatically, with multiple life-prolonging agents now available for treating the disease. Docetaxel was the first agent shown to improve life expectancy, as demonstrated by the TAX 327[2] and SWOG 9916[3] trials. Since then, survival benefit in both the pre- and post-docetaxel setting has been demonstrated for abiraterone acetate[4,5] and enzalutamide,[6,7] and in the post-docetaxel setting, cabazitaxel[8] and radium 223[9] have shown improved survival. Clinicians struggle with how to optimally sequence these agents and are concerned that as patients progress through multiple lines of therapy, efficacy may be reduced, but toxicities will remain.

Abiraterone acetate was approved in Canada in July 2011 for men with mCRPC in the post-docetaxel setting and in May 2013 for the pre-docetaxel indication. Thus, in this report by Saad et al, we can assume that the 25 men treated with abiraterone all received it in the post-docetaxel setting. Patients treated with cabazitaxel all enjoyed a good performance status, but their clinical characteristics suggest their disease was not indolent. Twenty-five percent of the population had visceral metastases and 25% were treated with cabazitaxel after rapid progression post-docetaxel (within three months). Men who had received abiraterone tended to be older, not surprisingly, often given the reluctance to treat men with cytotoxic chemotherapy if they are older. However, the prior use of abiraterone did not impact on the utility of cabazitaxel in this population in terms of prostate-specific antigen (PSA) response rate, quality of life (QoL) improvements, or safety.

It is important to note that patient selection is still critical when using cabazitaxel or other cytotoxic agents. In the current study, approximately one-third of individuals stopped cabazitaxel for adverse events, but importantly, there were no treatment-related deaths. It is notable that 30% received prophylactic granulocyte colony-stimulating factor (GCSF) to reduce the risk of severe and/or febrile neutropenia, something which was not done in the pivotal TROPIC[8] trial. The feasibility of this strategy will vary across jurisdictions in Canada, where routine use of these agents is not always available for individuals whose treatment intent is not curative. On the opposite side of the coin, however, a quarter of individuals experienced improvements in their pain, and overall, approximately 40% had a PSA response that was not affected by prior abiraterone exposure. There were also improvements noted in QoL, as measured by validated questionnaires. Thus, cabazitaxel in the post-docetaxel setting, irrespective of prior abiraterone exposure, is an active agent, but must be used in appropriately selected patients.

It is comforting for clinicians managing these patients to see that the efficacy of cabazitaxel is maintained in patients with prior abiraterone exposure. With the plethora of new agents available for managing this disease, many questions have arisen as to how sequencing and multiple lines of therapy may affect the utility of subsequent agents. As an example, there were initial reports that the efficacy of docetaxel given after prior abiraterone exposure may be significantly worse than reported in the original pivotal trials,[10] but in other larger reports, such as a post-hoc analysis of the COUGAR 302 trial, this has not borne out.[11] Thus, this report by Saad et al gives us comfort that the use of cabazitaxel in a third-line setting still has activity and tangible benefits for patients.

The authors note the limitations of their study due to its non-randomized design, small sample size, and post-hoc analysis. Also, there is no report on survival outcomes for these patients so it is unknown whether the PSA and QoL response rates have translated into improvements in overall disease control and life expectancy for patients. Nonetheless, in an incurable setting, improvements in QoL are valuable for patients and justify the use of cabazitaxel in this population.

It is also important to note that this study does not address the optimal sequence of how these agents should be administered. This will become an ever increasingly complicated question to answer now that early administration of docetaxel in metastatic hormone-sensitive patients is commonly occurring based on the CHAARTED[12] and STAMPEDE[13] data. Some of these questions may only be answerable by using real-world databases. It behooves clinicians and partners to come together on a national level to create these databases to demonstrate outcomes for patients so that they have access to all life-prolonging therapies; this is currently not the case in all Canadian jurisdictions. It has been done already in kidney cancer with the Canadian Kidney Cancer Information System and there is no reason that it can't also be done in prostate cancer.

The treatment of mCRPC in the last decade has seen massive change. We now have multiple agents that improve survival, including hormonal agents, cytotoxics, and radioistopes. We must not forget that despite our enthusiasm for the new hormonal agents, abiraterone and enzalutamide, there is still a place for cytotoxic agents, such as docetaxel and cabazitaxel. In order to optimize patient outcomes, we must work as multidisciplinary teams in order to provide appropriate patients an opportunity to have access to all life-prolonging therapies.

Competing interests: Dr. North has received grants/honoraria from Astellas, Janssen, Novartis, Pfizer, and Sanofi; and has participated in clinical trials with Astellas, Lilly, Janssen, Merck, Novartis, Roche, and Sanofi.

References

1. Saad F, Winquist E, Hubay S, et al. Efficacy, quality of life, and safety of cabazitaxel in Canadian metastatic castration-resistant prostate cancer patients treated or not with prior abiraterone. *Can Urol Assoc J* 2016;10(3-4):102-9. http://dx.doi.org/10.5489/cuaj.3470
2. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-12. http://dx.doi.org/10.1056/NEJMoa040720
3. Petrylak D, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; 351:1513-20. http://dx.doi.org/10.1056/NEJMoa041318
4. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995-2005. http://dx.doi.org/10.1056/NEJMoa1014618
5. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013;368:138-48. http://dx.doi.org/10.1056/NEJMoa1209096
6. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367(13):1187-97. http://dx.doi.org/10.1056/NEJMoa1207506
7. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424-33. http://dx.doi.org/10.1056/NEJMoa1405095
8. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomized open-label trial. *Lancet* 2010;376:1147-54. http://dx.doi.org/10.1016/S0140-6736(10)61389-X
9. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213-23. http://dx.doi.org/10.1056/NEJMoa1213755
10. Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: Clinical evidence for cross-resistance? *Ann Oncol* 2012;23:2043-7. http://dx.doi.org/10.1093/annonc/mds119
11. De Bono J, et al. 2015 Genitourinary Cancer Symposium, San Francisco, CA; abstract 184.
12. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737-46. http://dx.doi.org/10.1056/NEJMoa1503747
13. James N et al. ASCO 2015 Annual Meeting, Chicago, IL; abstract 5001.

Correspondence: Dr. Scott North, Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, AB, Canada; Scott.North@albertahealthservices.ca