CUA-CUOG CRPC Guidelines: A useful compendium

Joseph L. Chin, MD, FRCSC

Division of Urology, London Health Sciences Centre, Western University, London, ON

See related article http://dx.doi.org/10.5489/cuaj.2526.

Cite as: *Can Urol Assoc J* 2015;9(3-4):E224-5. http://dx.doi.org/10.5489/cuaj.2873
Published online April 13, 2015.

Until recently, the urologist's active involvement in the care of a patient with advanced prostate cancer is confined to the administration of androgen deprivation therapy (ADT). With the development of castration resistance, the urologist either initiates a referral to a medical oncologist or simply continues with ADT through inexorable disease progression and the eventual demise of the patient. Following a prolonged draught, there has been a recent deluge of approved therapeutic agents for advanced stage prostate cancer, thanks to several positive clinical trials yielding high-level evidence and strong recommendations on which to base management decisions (TAX- 327, COU-301, AFFIRM, COU-302, PREVAIL, TROPIC, ALSYMPCA etc).

The 2015 joint-CUA-CUOG Guidelines document for the management of castration-resistant prostate cancer (CRPC), coauthored by a multi-disciplinary group of Canadian opinion leaders and published in this issue of *CUAJ*, is very timely and should serve as a practical up-to-date reference for urologists and oncologists.[1] The urologist can readily consult and navigate through the document based on the patient's status: non-metastatic versus metastatic, chemotherapy naïve versus post-chemotherapy, prior treatment versus no exposure to any androgen receptor (AR) targeted therapy, and minimal/no symptoms versus symptomatic.

However, in spite of this cornucopia of new evidence and options, much remains to be researched.

The concluding sentence of the document rightly states: "Because CRPC remains an incurable and ultimately fatal illness, inclusion of patients in clinical trials remains paramount."[1] For instance, as stated in the Guidelines, there is no standard of care and no approved regimen in M0 CRPC. "M0" is logically an "ideal" stage for Phase I, II and III trials because typically patients are asymptomatic, with excellent performance status and can usually tolerate and complete the investigational therapy well. Most importantly, patients are more likely to accept double-blind randomization at this stage, since they correctly perceive "they have little to lose," even if randomized to the placebo arm.

Still with M0 CRPC, the Guidelines document states "the role of magnetic resonance imaging (MRI) and positron emission tomography (PET) is unclear."[1] Although beyond the mandate and scope of this exercise, the evolving role and utility of newer imaging modalities such as MRI, PET, and especially co-registered imaging such as PET/computed tomography (CT), in the detection of skeletal and visceral metastases, merit some discussion. Traditionally, the definition of "M0" disease is based on negative findings on conventional planar bone scintigraphy and for visceral metastases, CT. Changes from metastatic osseous disease on MRI, in fact, occur early and can be visible as displacement of bone marrow, denoted by signal loss on T1, in contrast to surrounding uninvolved fat marrow tissue with high signals. Thus MRI has been shown to out-perform bone scan in the detection of early "occult" osseous metastases. Similarly, ^{18}F-choline PET and ^{11}C-choline PET have both been shown to identify more patients with osseous metastases than standard ^{99m}Tc-MDP bone scan, since their radioactive tracer is fixed at the bone involvement site. Furthermore, co-registered imaging, such as PET/CT, provides superior functional and anatomic information for more accurate staging of advanced prostate cancer,[2] facilitating proper choice of therapy.

Another important statement in the Guideline document is "The optimal sequence of available options remains unknown."[1] In the absence of reliable predictive biomarkers, the clinician faces a grave challenge of identifying patients who would likely derive more benefit from the novel AR-targeted agents or from chemotherapeutic agents, thus affecting the initial choice of therapy. An example of a promising marker is AR-V7 found in circulating tumour cells.[3] Androgen receptor splice variant-7 is a truncated

form of the AR without the ligand-binding domain (the therapeutic target of abiraterone as well as enzalutamide). Prostate cancer which expresses AR-V7 has been shown to respond poorly to both abiraterone and enzalutamide, and hence this biomarker may be useful as a therapeutic guide.[3] Compounding the challenge for clinicians is the fact that exposure to certain agents and progression in disease course often both lead to altered expression of various biomarkers and altered tumour response to various drugs, which then affects the choice of second-and third-line therapy. Ongoing research in predictors of response and mechanisms of resistance should hopefully help determine the choice and the optimal sequence of therapy.

This Guidelines document should serve as a useful compendium for urologists and oncologists who manage patients with advanced, and in particular, CRPC. However, to generate more high-level evidence leading to further improvement in patient care and outcome, the importance of clinician engagement, as well as encouragement of patient participation, in clinical trials has to be emphasized.

Competing interests: Dr. Chin declares no competing financial or personal interests.

References

1. Saad F, Chi KN, Finelli A, et al. The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC). *Can Urol Assoc J* 2015;9:90-6. http://dx.doi.org/10.5489/cuaj.2526
2. Jambor I, Kuisma A, Ramadan S, et al. Prospective evaluation of planar bone scintigraphy, SPECT, SPECT/CT, 18F-NaF PET/CT and whole body 1.5T MRI, including DWI, for the detection of bone metastases in high risk breast and prostate cancer patients: SKELETA clinical trial. *Acta Oncol* 2015;1-9. http://dx.doi.org/10.3109/0284186X.2015.1027411
3. Antonarakis ES, Lu CX, Wang H, et al.: AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer. *N Engl J Med* 2014;371:1028-38.

Correspondence: Dr. Joseph Chin, E2-650, 800 Commissioners Rd. E., London Health Sciences Centre, London ON N6A 4G5; fax 519 685-8455; joseph.chin@lhsc.on.ca