

UPDATE – 2021 Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) castration-resistant prostate cancer (CRPC) guideline: What has changed since 2019?

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In 2019, the Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) castration-resistant prostate cancer guideline was published to highlight the evolving landscape in castration-resistant disease, especially with the advent of therapeutic options for patients with high-risk, non-metastatic CRPC. At the time of publication, apalutamide and enzalutamide had received Health Canada approval and were included in the 2019 guideline. The results of darolutamide studies had just been reported, briefly summarized in the text, but darolutamide not officially recommended for use, given the lack of Health Canada approval at that time. Since then, darolutamide has been approved in Canada and important new data has been published for all three agents, which are now part of the 2021 updated guideline. For metastatic CRPC, the poly-ADP ribose polymerase (PARP) inhibitor olaparib has also recently been approved in Canada and the target population is described in the new guideline. Lastly, regarding the use of radium-223, additional updated safety information has been included in the 2021 guideline.

This brief review summarizes some the changes, the reasons that justify them, as well as some thoughts as to the importance of ensuring optimal care for patients with CRPC.

Non-metastatic CRPC

Three effective treatment options

For men with high-risk non-metastatic (nm)CRPC, defined as a prostate-specific antigen (PSA) doubling time (PSADT) of less

than 10 months, with an estimated life expectancy of greater than five years should be offered apalutamide, enzalutamide, or darolutamide (Level 1, Strong recommendation).

This strong recommendation is based on the fact that the three agents have shown a significantly longer metastases-free survival, a longer time to PSA progression (i.e., resistance to therapy), and most importantly, a longer overall survival. This is even though these patients were followed closely and generally treated very early with effective life-prolonging therapies in the placebo arm. The trials clearly support the evidence that earlier is better in patients treated with hormonally based therapy in the CRPC state, with or without visible metastases. The evidence is also supported by the findings that enzalutamide and apalutamide in the metastatic castration-sensitive prostate cancer (CSPC)/metastatic hormone-sensitive prostate cancer (HSPC) state also significantly improved survival regardless of the extent of metastatic disease.

Bone health in the non-metastatic patient

Increased rates of fractures have been observed with all androgen receptor-axis-targeted therapies (ARATs). Although it is unlikely that these agents are themselves responsible for the increased rates of fractures, patients treated with ARATs will remain on androgen deprivation therapy (ADT) and non-metastatic for much longer than in the past. Properly evaluating these patients and considering bone-supportive agents to prevent the risk of fractures should be a priority, along with maximal cancer control.

Metastatic CRPC

The addition of olaparib in the treatment options for mCRPC

Olaparib 300 mg twice daily is recommended for patients with mCRPC and homologous recombination repair (HRR)

mutation who have progressed on a previous ARAT (Level 1, Strong recommendation).

Olarib, a PARP inhibitor, is the first agent to show a progression-free and overall survival advantage using a biomarker-based approach to identify patients for treatment. The Health Canada approval is for patients that harbor BRCA1, BRCA2, and ATM mutations. This is the first in this class of agents and others are being tested in mCRPC in the second- and third-line settings. Trials are also underway to determine if PARP inhibitors in the first-line mCRPC setting, in combination with abiraterone and enzalutamide, would be more effective compared to standard of care abiraterone and enzalutamide alone. These trials include patients without HRR mutations to see if they may also benefit from a combined approach.

Radium-223 in combination with ARAT and bone health considerations

Radium-223 should not be combined with abiraterone. A bone-supportive agent (denosumab or zoledronic acid) should always be used when using radium-223 (Level 1, Strong recommendation).

This strong recommendation is based on a phase 3 study in the first-line mCRPC setting that compared radium-223 in combination with abiraterone/prednisone vs. abiraterone/prednisone alone; the study showed no advantage and an increased risk of fractures with the combination treatment. Trials are underway that combine enzalutamide to radium-223. **For the time being, radium-223 should not be combined with any other life-prolonging agent used for mCRPC.** Importantly, **all patients should receive bone-supportive therapy to reduce the risk of fractures when radium-223 is used.**

Considerations for sequencing in CRPC

Until recently, prostate cancer patients would receive only ADT until their cancer progressed to mCRPC; it was only at this point that patients would access additional therapy. With the growing evidence of effective and life-prolonging therapy prior to developing mCRPC, sequencing when patients do progress to mCRPC needs to consider what patients had received previously. Trials are ongoing to introduce ARATs in the locally advanced/high-risk or PSA-recurrent non-metastatic state may further improve outcome but will also further challenge the sequencing issue when patients eventually progress.

Basic principles support a change in mechanism of action or class of agent when patients progress on therapy. **There is little data to support the re-use of an ARAT once patients have progressed.** This general approach is supported by the CARD and PROFOUND trials, which used a re-exposure of an ARAT as the control arm of the studies. **A median time to progression of less than four months was observed when patients were re-treated with an ARAT;** however, a small subset of patients may have longer, more substantial responses, and efforts are underway to identify who those patients might be. **In the CARD study, cabazitaxel was shown to be superior in the third-line setting following ARAT and docetaxel, rather than returning to an ARAT.** Importantly, several sequencing trials are underway using many novel agents, including radio-ligand therapy, immunotherapy, and other specific targets.

Conclusions

The changing therapeutic landscape of advanced prostate cancer will require regular updates to ensure that patients at high risk of suffering and dying from, rather than with, prostate cancer are optimally managed in Canada. As effective therapeutics are introduced earlier in the patient journey, the need to establish biologically rational and (hopefully) evidence-based sequencing becomes critically important. Until then, patients with CRPC should be treated in multidisciplinary settings and should always be considered for clinical trials. In so doing, we will ensure optimal care for our patients and continue our contribution in moving the field forward.

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