

2022 UPDATE: Canadian Urological Association-Canadian Urologic Oncology Group guideline: Metastatic castration-naïve and castration-sensitive prostate cancer

Summary of changes

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Cite as: So AI, Saad F. 2022 UPDATE: Canadian Urological Association-Canadian Urologic Oncology Group guideline: Metastatic castration-naïve and castration-sensitive prostate cancer – Summary of changes. *Can Urol Assoc J* 2022;16(12):389-91. <http://dx.doi.org/10.5489/cuaj.8159>

Full-text available at cuaj.ca and cua.org. This is an update of a CUA guideline originally published online December 5, 2019, and in print in February 2020.

Introduction

The most recent Canadian Urological Association-Canadian Urologic Oncology Group guideline on metastatic castration-naïve and castration-sensitive prostate cancer (mCNPC/mCSPC) was published in 2020.¹ New data in this patient population have prompted an update to the guideline in order to add treatment options that have proven to improve disease progression and overall survival (OS). This brief review summarizes the changes in the guideline, as well as the importance of ensuring proper treatment intensification in addition to androgen deprivation therapy (ADT) in patients with metastatic hormone-naïve or castration-sensitive prostate cancer.

Systemic therapies: Chemotherapy, abiraterone acetate, enzalutamide, and apalutamide

Triplet therapy

In patients who can safely tolerate docetaxel and in whom docetaxel is felt to be appropriate, triplet regimen should be considered as a treatment option.

2022 UPDATES

In patients who can safely tolerate docetaxel and in whom docetaxel is felt to be appropriate, triplet regimen should be considered as a treatment option.

- UPDATE #1: Abiraterone acetate plus prednisone in combination with docetaxel is a treatment option for patients with mCNPC/mCSPC in high-volume of disease (*Level of evidence 1, Strong recommendation*).
- UPDATE #2: Abiraterone acetate plus prednisone in combination with docetaxel may be considered for patients with mCNPC/mCSPC with low-volume disease (*Level of evidence 2, Weak recommendation*).
- UPDATE #3: Darolutamide in combination with docetaxel is a treatment option for patients with mCNPC/mCSPC regardless of volume of disease (*Level of evidence 1, Strong recommendation*).
- UPDATE #4: Patients with mCNPC/mCSPC should be assessed in a multidisciplinary manner (*Level of evidence 3, strong recommendation*).

Update #1

Abiraterone acetate plus prednisone in combination with docetaxel is a treatment option for patients with mCNPC/mCSPC in high-volume of disease (*Level of evidence 1, Strong recommendation*).

Update #2

Abiraterone acetate plus prednisone in combination with docetaxel may be considered for patients with mCNPC/mCSPC with low-volume disease (*Level of evidence 2, Weak recommendation*).

Recent data from the PEACE-1 trial showed the benefits of the combination of ADT and abiraterone acetate plus prednisone and docetaxel compared to docetaxel and ADT.² In a 2×2 factorial design, patients with de novo mCSPC (n=1173) were randomly assigned to receive standard of care (SOC) (n=296), SOC plus abiraterone and prednisone (n=29), SOC plus radiotherapy (n=293), or SOC plus abiraterone plus radiotherapy (n=291). SOC treatments included ADT with or without docetaxel, and overall, 60% of participants received a median of six cycles of docetaxel.

Compared with SOC (including docetaxel) without abiraterone, the addition of abiraterone improved the median OS and reduced the relative risk of death from any cause by 25% (adjusted hazard ratio [HR] for OS 0.75, 95.1% confidence interval [CI] 0.59–0.95, p=0.017). Using CHAARTED study criteria, patients with high-volume disease treated with abiraterone and prednisone with SOC (including docetaxel) compared to SOC alone reduced the relative risk of radiographic progression or death (adjusted HR 0.47, 99.9% CI 0.30–0.72, p<0.0001); OS was improved from 3.47 years with SOC without abiraterone to 5.14 years when abiraterone was added, corresponding to a 28% reduction in relative risk of death (adjusted HR 0.72, 95.1% CI 0.55–0.95, p=0.019).

In patients with low-volume disease, the addition of abiraterone to SOC reduced the relative risk of radiographic progression or death (adjusted HR 0.58, 99.9% CI 0.29–1.15, p=0.0061); OS benefits were not found due to lack of maturity of the data (median OS not reached in either group). Importantly, although the addition of abiraterone to SOC increased the risk of hypertension (22% vs. 13%), the combination did not significantly increase grade 3 adverse events or other severe adverse events, such as neutropenia or fatigue.

Update #3

Darolutamide in combination with docetaxel is a treatment option for patients with mCNPC/mCSPC regardless of volume of disease (*Level of evidence 1, Strong recommendation*).

The ARASENS trial randomized 1306 mCSPC patients to receive docetaxel and ADT with (n=651) or without (n=655) darolutamide.³ A significant improvement in OS was observed in those receiving darolutamide; the risk of death was 32.5% lower in the darolutamide group than in the placebo group (HR 0.68, 95% CI 0.57–0.80, p<0.001), and OS at four years was 62.7% (95% CI 58.7–66.7) in

the darolutamide group and 50.4% (95% CI 46.3–54.6) in the placebo group. Although efficacy based on volume of disease was not defined, benefits of the addition of darolutamide with docetaxel was seen regardless of metastatic stage at initial diagnosis (M1: HR 0.71, 95% CI 0.59–0.85; M0: HR 0.61, 95% CI 0.35–1.05). The addition of darolutamide to docetaxel did not increase adverse events, such as neutropenia or fatigue; the addition darolutamide slightly increased the rate of rash (16.6% vs. 13.5%) and hypertension (13.7% vs. 9.2%).

Is there an “optimal” treatment option?

The ARASENS and PEACE-1 trials both show the benefits of adding an androgen receptor pathway inhibitor (ARPi) to docetaxel in CSPC. The studies show the benefits of triplet therapy (ADT, ARPi, and docetaxel) compared to ADT and docetaxel, but did not directly compare efficacy of triplet therapy to the combination therapy of ADT and ARPi. As such, these guidelines do not identify an “optimal” treatment option and various triplet or doublet treatments are recommended.

In subgroup analyses, both studies show that there are limited patient characteristics that may influence the use of triplet vs. doublet therapy, as benefits in OS and radiographic progression-free survival (rPFS) was seen in a majority of prespecified patient factors. One patient characteristic, tumor volume based on CHAARTED study criteria,⁴ was shown to be important in the PEACE-1 trial; in patients with low-volume disease, the addition of abiraterone to SOC reduced the relative risk of radiographic progression or death (adjusted HR 0.58, 99.9% CI 0.29–1.15, p=0.0061) but OS benefits seen in patients with high-volume disease were not found, likely due to lack of maturity of the data (median OS not reached in either group). The influence of tumor volume was not reported in the ARASENS trials, but survival benefit was seen regardless of stage of diagnosis.³ In summary, although volume of disease appears to differentiate survival advantage in the PEACE-1 trial, recommendations of triplet therapy, regardless of volume of disease, are made.

Importance of multidisciplinary consultation

Update #4

Patients with mCNPC/mCSPC should be assessed in a multidisciplinary manner (*Level of evidence 3, Strong recommendation*).

Timing of initiation and choosing the optimal systemic therapy from a multitude of options requires careful consideration of several different clinical factors, such as eligibility of chemotherapy, side effect profile of medications, disease

burden, symptoms, and presence of visceral metastases. Since treatment may require a multifaceted approach, including upfront docetaxel-based regimes, early assessment of eligibility of chemotherapy is essential. As well, combined opinions from urology, medical oncology, and radiation oncology may be required to provide optimal care of patients with mCNPC/mCSPC. Additionally, as mCNPC/mCSPC continues to be an incurable disease, strong consideration should be given to inclusion of patients in clinical trials.

Although there is substantial evidence of the benefits of intensifying treatments beyond ADT in mCNPC/mCSPC, there is recent evidence showing that there has been slow uptake of the addition of an ARPi or docetaxel to ADT in this patient population.^{5,6} These results show the importance of: the continued education of those diagnosing and treating prostate cancer, the consideration of referral to colleagues that use chemotherapy and ARPis, and the assessment of patients with mCNPC/mCSPC in a multidisciplinary manner. The use of opinions from urology, medical oncology, and radiation oncology will ensure optimal management of these patients.

Competing interests: Dr. So has been an advisory board member for AbbVie, Astellas, Bayer, Janssen, Merck, and TerSera. Dr. Saad has been an advisory board member for and has received payment/honoraria from Amgen, Astellas, AstraZeneca, Bayer, Janssen, Knight, Myovant, Novartis, Pfizer, Sanofi, and Tolmar; and has participated in clinical trials supported by Amgen, Astellas, AstraZeneca, Bayer, Janssen, Novartis, Pfizer, and Sanofi.

Prior to original publication, this guideline underwent review by the CUA Guidelines Committee, CUA members at large, and the CUA Executive Board. Updates were approved by the CUA Guidelines Committee and Executive Board.

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