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

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INTRODUCTION

Metastatic prostate cancer remains an incurable disease. In Canada, approximately 8% of men with prostate cancer are diagnosed *de novo* with metastatic disease, and, in 2018, roughly 1200 men were diagnosed with *de novo* metastatic prostate cancer (PC) (1). The mainstay of treatment for *de novo* metastatic PC is androgen deprivation therapy (ADT), either surgical or medical castration, which is initially effective in almost all patients. However, progression is inevitable, heralded by a rise in PSA, increasing disease burden and/or worsening symptoms, a disease state called metastatic castration resistant prostate cancer (mCRPC).

Men with metastatic PC have a poor prognosis with an estimated median overall survival of approximately 3-4 years (2). Compared to prostate cancer that develops metastases after diagnosis of localized disease, *de novo* metastatic prostate cancer has been shown to have a

worse overall prognosis (3, 4). Over the past decade, practice changing trials have demonstrated improved survival in men with metastatic castration-naïve /castration-sensitive prostate cancer (mCNPC/mCSPC) using ADT intensification strategies that includes both systemic therapy and treatment of the primary cancer.

The Canadian Uro-oncology Group (CUOG) in collaboration with the Canadian Urological Association (CUA) sought to provide management guidelines to optimize the treatment of patients with mCNPC/mCSPC.

METHODS

EmBASE and Medline databases were accessed to identify all relevant articles focused on mCNPC or mCSPC published between January 2000 and April 2022 with the following key words strategy: "prostate cancer", "hormone sensitive", "castration naïve", "castration sensitive", "androgen deprivation", "chemotherapy", "androgen receptor-axis targeted therapy", and "metastatic." An expert panel comprised of urologists, medical oncologists and radiation oncologists with significant experience managing mCNPC/mCSPC was utilized to develop the recommendations. Guidelines were developed by consensus among the panel. Levels of evidence and grades of recommendation employ the WHO modified Oxford Center for Evidence-Based Medicine grading system(5). Based on a modified GRADE methodology, the strength of each recommendation is represented by the words STRONG or WEAK(5). Wherever Level 1 evidence is lacking, the guideline attempts to provide expert opinion to aid in the management of patients.

INDICATIONS FOR STAGING IN PROSTATE CANCER

For patients with newly diagnosed prostate cancer, staging with computed tomogragph (CT) scans of the chest, abdomen and pelvis and bone scan (99mTc-MDP) should be performed for men with any high-risk features: PSA>20 ng/mL, Gleason score >7, clinical stage T3 or greater *(Level of evidence 3, Strong recommendation).*

Conventional imaging to stage PC includes, bone scintigraphy using technetium-99mmethylene diphosphonate (99mTc-MDP) to assess for bone metastases and abdominopelvic CT imaging to assess for lymphadenopathy and visceral metastases. In patients with high risk disease, CT imaging of the chest may also be considered as lung metastases are the most common site of visceral metastases (6).

Novel diagnostic imaging to stage PC, particularly PSMA-targeted PET/CT, improve the sensitivity and specificity of conventional imaging; however, these tests are not universally available Canada and they are still considered investigational by Health Canada. Most importantly, all of the phase 3 trials in mCNPC/mCSPC utilized conventional imaging for staging and risk determination, and conclusions were based on these.

ASSESSMENT OF PROGNOSIS

Patients diagnosed with metastatic prostate cancer should be classified as high volume/high risk or low volume/low risk based on conventional imaging and prostate cancer biopsy for prognostication *(Level of evidence 2, Weak recommendation).*

Recent clinical trials of patients with mCNPC/mCSPC have used pragmatic prognostic factors to stratify prognosis. The CHAARTED trial classified PC based on volume of disease. 'High volume' was defined by the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis, and 'low volume' was defined as all other mCNPC/mCSPC (7). The LATITUDE trial classified 'high risk' patients based on three different criteria: visceral metastases, ≥ 3 bony metastases or Gleason score ≥ 8; high risk was defined as having 2 or more of these criteria whereas low risk was defined having less than 2 (8). Interestingly, a comparative study of the classification of each of these trials showed an overall discordance of 18.2% between the CHAARTED and LATITUDE criterion; however, it appears that disease burden (defined radiologically or by PSA) and high-grade tumors portend a worse prognosis (9).

ANDROGEN DEPRIVATION THERAPY

ADT should be started on patients with newly diagnosed with metastatic PC *(Level of evidence 1, Strong recommendation).*

Continuous ADT is the standard of care for patients with metastatic PC while intermittent may be considered in select patients.

Androgen receptor signaling plays a key role in the progression of PC, and thus *de novo* mCNPC remains highly driven by testosterone. Hence, the primary step in the management of mCNPC, which remains the backbone of treatment for all men with metastatic PC until death, is androgen deprivation therapy (ADT). ADT can be achieved by surgical castration (orchiectomy) or pharmacologically with agents that inhibit Leydig cell production of testosterone (GnRH agonists or GnRH antagonists). The optimal timing of androgen deprivation has been the subject of many trials with two systematic reviews suggesting early treatment is associated with improved overall and cancer-specific survival and decreases the rate of skeletal events compared to deferred treatment (10, 11). More importantly, the early treatment of mCNPC with ADT is required if other systemic treatment such as docetaxel or androgen receptor axis inhibitors are used.

ADT is associated with side effects, and may increase the risk of cardiovascular events but evidence has been contradictory. Intermittent androgen suppression (IAS) that cycles androgen deprivation treatment based on prostate specific antigen (PSA) values has been shown to improve quality of life; however, continuous ADT should be utilized in mCNPC and IAS only used as an exception in select patients with close follow-up (12, 13). As well, the benefit of

combined treatment of mCNPC with additional systemic therapy was demonstrated in the context of continuous ADT.

LOCAL THERAPY: TREATMENT OF THE PRIMARY CANCER IN MCNPC

Patients with low volume metastatic disease burden of prostate cancer should be considered for external beam radiation to the prostate *(Level of evidence 2, Strong recommendation).*

In the context of low volume mCNPC, treatment of the primary disease in the prostate has theoretical benefits, including reducing local side effects that may occur due to local disease progression as well as removing the cancer that could be the source of cytokines and growth factors that may induce disease progression(14).

Two recent randomized trials assessed the impact of external beam radiation therapy (EBRT) in mCNPC. The HORRAD trial randomized 432 men with mCNPC and PSA >20ng/mL to receive EBRT of the prostate with ADT or ADT alone. The initial prescribed dose was 70 Gy in 35 fractions of 2 Gy, during an overall treatment time of 7 weeks. During the study period, an optional schedule considered biologically equivalent was added and consisted of a dose schedule of 57.7 Gy in 19 fractions of 3.04 Gy, three times a week for 6 weeks. At baseline, the median PSA was 142 ng/ml and 67% of patients had more than five bone metastases. No significant difference was found in overall survival (OS) (hazard ratio (HR), 0.90; 95% CI: 0.70–1.14; p = 0.4), but there was a benefit to median time to PSA progression in the radiotherapy group (15 months vs 12 months, crude HR, 0.78; 95% CI: 0.63–0.97; p = 0.02). Subgroup analysis showed that mCNPC with < 5 metastases (HR, 0.90, 95% CI: 0.70-1.14, p=NS) and no bony pain (HR, 0.83, 95% CI: 0.69-1.14, p=NS) appeared to have the most benefit of EBRT.

The STAMPEDE trial, also known as MRC PR08, is a multi-arm multi-stage (MAMS) randomized trial recruiting in the United Kingdom and Switzerland. It aimed to evaluate multiple therapeutic strategies in the management of high-risk locally advanced and mCNPC compared to standard of care (androgen deprivation only). In the EBRT component of the study, the trial randomized 2061 men with mCNPC to either EBRT and ADT or ADT alone(15). The median PSA was 97 ng/mL, and 819 (40%) men had low metastatic burden based on CHAARTED criteria and 1664 (81%) had no pain (7, 15). EBRT was given as one of two schedules: either 36 Gy in six consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2.75 Gy over 4 weeks. Subgroup analyses were pre-specified for baseline metastatic burden (low vs high). Similar to the HORRAD trial, EBRT improved failure-free survival (FFS) (HR, 0.76, 95% CI 0.68–0.84; p<0.0001) but not OS (0.92, 0.80–1.06; p=0.266). Subgroup analysis by metastatic burden showed FFS was improved in both low and high metastatic burden (low metastatic burden, HR, 0.59, 95% CI 0.49–0.72; p<0.0001 and metastatic burden, interaction p=0.002; HR, 0.88, 95% CI 0·77–1·01; p=0·059). Overall survival was improved in patients with low metastatic burden at baseline who were allocated EBRT (HR, 0.68, 95% CI 0.52–0.90; p=0.007)

whereas in patients with a high metastatic burden, there was no impact on OS (HR, 1.07, 95% CI 0.90–1.28; p=0.420).

Although both trials showed a lack of benefit of EBRT in unselected men in mCNPC, both HORRAD and STAMPEDE reveal the benefits of local therapy in those with low burden disease. A recent STOPCAP meta-analysis combining data from the trials confirm the benefits of EBRT in men with fewer than five bone metastases (16). This meta-analysis showed that there was 7% improvement in 3-yr survival in men with fewer than four bone metastases.

Radical prostatectomy in mCNPC should only be performed in a clinical trial setting (Expert opinion, Strong recommendation)

Currently, there is limited evidence showing the benefit of radical prostatectomy in mCNPC. However, the results from HORRAD and STAMPEDE imply that there may also be certain men with mCNPC that may benefit from surgical extirpation. There are many clinical trials currently assessing this question, including TRoMBONE (Testing radical prostatectomy in men with PC and oligometastases to the bone: a randomized controlled feasibility trial)(17), SWOG1802 (Standard systemic therapy with or without definitive treatment in treating participants with metastatic PC- https://www.swog.org/clinical-trials/s1802), G-RAMPP/AUO –AP-75/13 (Impact of radical prostatectomy as primary treatment in patients with PC with limited bone metastases)(18), and IP2-ATLANTA (Additional Treatments to the Local tumour for metastatic prostate cancer-Assessment of Novel Treatment Algorithms (IP2-ATLANTA): protocol for a multicentre, phase II randomised controlled trial)(19). . Until the results of these trials clarify the impact of radical prostatectomy in mCNPC and more importantly which patients that would benefit the most, surgery of the primary is not recommended in patients with metastatic PC.

SYSTEMIC THERAPIES: CHEMOTHERAPY, ABIRATERONE ACETATE, ENZALUTAMIDE, AND APALUTAMIDE

Docetaxel (75 mg/m^2 every 3 weeks for six cycles) plus ADT is an option for patients with mCNPC/mCSPC, good performance status and high-volume metastatic disease defined as: presence of visceral metastases, or four or more bone lesions with at least one beyond the vertebral bodies and pelvis *(Level 1, Strong recommendation).*

Docetaxel plus ADT may also be an option for patients with mCNPC/mCSPC and good performance status with low volume disease *(Level 2, Weak recommendation).*

Consideration of patients with "high risk" mCNPC/mCSPC (defined as at least two of: Gleason score of 8–10, visceral metastases and 3 or more bone metastases) and good performance status can also be considered for docetaxel chemotherapy (*Level 1, Strong recommendation).*

Docetaxel, a taxane derivative that binds to tubulin that inhibits mitosis and tumour proliferation, was the initial chemotherapeutic agent that improved survival in men mCRPC (20). Three different large randomized trials assessed the impact of introducing docetaxel in mCNPC/mCSPC: CHAARTED, STAMPEDE, and GETUG-AFU 15(7, 21, 22). The CHAARTED trial randomized 790 with mCNPC/mCSPC patients to ADT plus docetaxel (75 mg/m^2 every 3 weeks for six cycles) or ADT alone (7). Within this trial, 35% (n=277) had low volume metastases and 65% (n=513) had high volume metastases (high volume of metastases was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis). Overall, the median OS was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 months vs. 44.0 months; HR, 0.61; 95% CI 0.47-0.80; P<0.001). Subgroup analysis showed that OS benefits of combination there were maintained in the high volume mCNPC/mCSPC (n=513, HR, 0.63 (95% CI, 0.50–0.79) P<0.001) whereas survival benefits were lost in low volume disease (n=277, HR, 1.04 (95% CI, 0.70-1.55) P=0.86)(23).

The GETUG-AFU15 trial randomized 385 patients with mCNPC/mCSPC to receive ADT plus docetaxel or ADT alone (22). Although the dosage of docetaxel was the same as in CHAARTED, patients were allowed to receive up to nine cycles compared to the six cycles in CHAARTED. There was no survival difference between the groups (58.9 months in the combined group vs 54.2 months in the ADT alone group, HR, 1.01, 95% CI 0.75–1.36). The differences in the outcomes of the two studies is likely due to the differences in the burden of disease in the two studies. Although 65% of patients in CHAARTED had high volume metastases, only 48% in the docetaxel arm of GETUG-AFU15 had high-volume disease. An unplanned post-hoc analysis of the high-volume cohort of GETUG-AFU 15 showed a non-significant trend toward improved OS in this cohort (39.8 months vs 35.1 months, HR, 0.78, 95% CI, 0.56-1.09) (24). A recent pooled analysis of both studies confirms the benefit of combined docetaxel and ADT in high-volume disease and lack of benefit on low-volume metastatic burden (25).

The third trial to assess the impact of docetaxel in mCNPC/mCSPC was the docetaxel component of the STAMPEDE trial(21). Unlike CHAARTED and GETUG-AFU15 trials, patients with high-risk non-metastatic PC were included. Eligible patients included: newly diagnosed metastatic, node positive, or high-risk locally advanced (with high-risk features defined as at least two of: T3/4, Gleason score of 8–10, and PSA ≥40 ng/mL) prostate cancer; or previously treated with radical surgery and/or radiotherapy with high-risk features. Of the 2962 patients randomized, 1817 (61%) patients had bony metastases and 592 patients received only ADT and six cycles of docetaxel (75 mg/m^2 every 3 weeks for six cycles). The combination of ADT and docetaxel had a survival advantage compared to ADT alone (HR, 0.78, 95% CI, 0.66–0.93; p=0.006). Although patients were not classified having high or low volume metastases, only patients with metastatic disease had evidence of benefit with ADT and docetaxel (HR, 0.76, 95% CI, 0.62–0.92; p=0.005).

A post-hoc non-prespecified analysis of STAMPEDE was published(26). Metastatic burden was assessable in only 76% of patients for the analysis (830 of 1086 patients) and 362 (44%) had low and 468 (56%) high metastatic burden. Although overall survival was neither statistically significant in low burden nor in high burden disease (HR, 0.76, 95% CI, 0.54-1.07; p=0.107 vs HR, 0.81, CI, 0.64-1.02, p=0.064), the authors found no evidence of heterogeneity of docetaxel effect between metastatic burden sub-groups (interaction p=0.827). The authors concluded that upfront docetaxel should be considered for patients with mCNPC/mCSPC regardless of metastatic burden. This retrospective analysis contradicts the results of CHAARTED, but the authors point out that this may be due to the larger number of patients with *de novo* mCNPC/mCSPC (n=362) in the low burden group compared to the low burden group in the CHAARTED trial (n < 160).

A recent meta-analysis of CHAARTED, GETUG-AFU15, and STAMPEDE confirms the benefit of addition of docetaxel to ADT for patients with mCNPC/mCSPC (HR, 0.77, 95% CI, 0.68–0.87, p<0.0001). The authors of the meta-analysis show that this translates to an absolute improvement in 4-year survival of 9%.

Abiraterone acetate (1000mg daily) with prednisone (5mg daily) plus ADT is an option for patients with mCNPC with at least two of the three: (Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis) *(Level of evidence 1, Strong recommendation).*

Abiraterone acetate (1000mg daily) with prednisone (5mg daily) plus ADT may be considered for patients with low volume mCNPC *(Level of evidence 3, Weak recommendation).*

Abiraterone acetate is a prodrug of abiraterone which is a CYP17A1 inhibitor; CYP17A1 is expressed in and is required for androgen biosynthesis. Abiraterone acetate, when combined with prednisone, was initially shown to improve survival in mCRPC, both prior to and after docetaxel treatment (27, 28). Two trials, LATITUDE and STAMPEDE, assessed the impact of abiraterone in mCNPC/mCSPC (8, 29, 30). In the LATITUDE trial, 1199 patients were randomly assigned to either the abiraterone acetate (1000mg) plus prednisone (5mg) once daily orally and ADT vs ADT alone. Eligible patients included patients with mCNPC with at least two of three high-risk features (Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis except lymph node metastasis). Updated OS data with median follow-up of 51.8 months showed that OS was significantly longer in the abiraterone acetate plus prednisone group (median 53.3 months [95% CI 48.2–not reached]) than in the placebo group (median 36.5 months [95% CI 33.5–40·0]), with a hazard ratio of 0.66 (95% CI 0.56−0.78; p<0·0001). A post-hoc exploratory analysis of the impact of disease burden showed that OS was improved only in patients with high-volume disease (n=487 in the abiraterone acetate plus prednisone and ADT and 468 in the ADT only group, HR 0.62 (95% CI, 0.52−0.74; p<0·0001); however, only few patients had low-volume disease in this study (n=110 in the abiraterone

acetate plus prednisone and ADT and n=133 in the ADT only group, (HR 0.72, 95% CI 0.47−1.10; p=0·1242).

In the abiraterone component of the STAMPEDE trial, the efficacy of abiraterone acetate and prednisolone was assessed in men with mCNPC (29). In this study, 1917 patients with mCNPC were enrolled with: newly diagnosed and metastatic, node-positive, or high-risk locally advanced prostate cancer (with at least two of following: cT3 or cT4, a Gleason score of 8 to 10, or PSA level ≥40 ng/mL) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (PSA >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse). Men were randomized to receive abiraterone acetate (1000mg daily) plus prednisolone (5mg) plus ADT or ADT alone. 52% of the patients had metastatic disease, 20% had node-positive or node-indeterminate non-metastatic disease, and 28% had node-negative, non-metastatic disease; 95% had newly diagnosed disease. In a subgroup analysis, the overall survival benefit was seen in PC patients with metastatic disease (HR 0.61, 95% CI 0.49–0.75) but not patients with non-metastatic high-risk prostate cancer(HR 0.75, 95% CI 0.48–1.18) (29). The impact of volume tumor burden was not reported.

A recent unplanned post-hoc analysis of 759 evaluable patients with bone metastases in the STAMPEDE trial were reclassified using CHAARTED “high or low volume” criterion or LATITUDE “high or low risk” criterion (31). Men with mCNPC had OS benefit with the addition of abiraterone acetate and prednisone to ADT irrespective of risk stratification for “risk” or “volume”. Using CHAARTED criteria, low volume HR was 0.66 (95% CI, 0.44-0.98) and high volume HR was 0.54 (95% CI 0.41-0.70); using the LATITUDE criteria, low risk HR was 0.64 (95% CI, 0.42-0.97) and high risk HR was 0.60 (95% CI, 0.46-0.78). Although these results are intriguing, the retrospective nature of the reclassification of risk and tumor volume is a significant limitation and thus the results can only be considered hypothesis generating.

Enzalutamide (160mg/day) is a treatment option for patients with mCNPC/mCSPC regardless of volume of disease *(Level of evidence 1, Strong recommendation).*

Enzalutamide should not be used in combination (concurrent use) with docetaxel to treat patients mCNPC/mCSPC *(Level of evidence 2, Strong recommendation).*

Enzalutamide may be considered in patients with mCSPC previously treated with docetaxel chemotherapy (sequential use) *(Level of evidence 1, Weak recommendation).*

Enzalutamide binds to the androgen receptor (AR) and inhibits the AR nuclear translocation and interaction with DNA. Suppression of the AR with enzalutamide was initially shown to improve survival in docetaxel naïve or treated mCRPC (32, 33). Two recent studies assessed the role of enzalutamide for patients with mCNPC: ARCHES and ENZAMET (34, 35). The ARCHES trial randomized 1150 patients with mCNPC/mCSPC to either enzalutamide (160mg/day) plus ADT or placebo plus ADT. The primary endpoint was radiologic progression free survival (rPFS),

defined as the time from randomization to the first objective evidence of radiographic disease progression or death. The combination of enzalutamide plus ADT improved rPFS compared to placebo-ADT (HR= 0.39; 95% CI, 0.30 - 0.50; P = 0.001; median not reached v 19.0 months). A recent final analysis showed improved overall survival in the enzalutamide treatment arm (HR=0.66; CI, 0.53-0.81; p<0.0001). (36) Prior docetaxel of up to six cycles was allowed, and 18% (205) patients received at least one dose of docetaxel prior to randomization; subgroup analysis showed that rPFS benefit was seen in both, patients who were chemotherapy-treated and chemotherapy-naïve. Benefit with enzalutamide in rPFS and OS was seen regardless of disease burden and timing of metastases (*de novo* vs metachronous).

ENZAMET was an open –label clinical trial that randomized 1125 patients with mCNPC/mCSPC to receive ADT and enzalutamide daily (160mg) or a nonsteroidal antiandrogen (NSAA: bicalutamide, nilutamide, or flutamide) with a primary endpoint of OS. There was an OS benefit in the enzalutamide plus ADT arm compared to NSAA (hazard ratio = 0.67; 95% CI, 0.52 - 0.86; P = 0.002). Kaplan–Meier estimates of overall survival at 3 years were 80% in the enzalutamide group and 72% in the NSAA arm. Unlike ARCHES, concurrent use of docetaxel was allowed and decision to treat with chemotherapy was at the discretion of the investigator. Use of chemotherapy was well balanced between the two arms (45% of those receiving enzalutamide and 44% of those receiving a NSAA planned for early docetaxel use). In a subgroup analysis, the benefits of enzalutamide on OS appeared only in the group without planned early docetaxel use (concurrent docetaxel: HR, 0.9 with a 95% CI, 0.62-1.31, and no concurrent docetaxel: HR, 0.8 with a 95% CI, 0.59-1.07). Although the authors state that the study is underpowered and data is too immature to specifically answer whether or not combination docetaxel and enzalutamide is beneficial in mCNPC/mCSPC, these results show that this combination should not be used until further evidence is shown for its benefits.

Apalutamide (240mg) is a treatment option for patients with mCNPC/mCSPC regardless of volume of disease *(Level of evidence 1, Strong recommendation).*

Apalutamide inhibits the AR by preventing its nuclear translocation and DNA binding. The first large randomized clinical trial assessing apalutamide in mCNPC/mCSPC was the TITAN trial, which randomized 1052 patients with mCNPC/mCSPC (any) to receive apalutamide (240mg once daily) plus ADT or ADT alone. As well, 10.7% received previous docetaxel therapy and 37.3% had low-volume disease. With a median of 40.0 months of follow-up, rPFS at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (HR, 0.48; 95% CI, 0.39 - 0.60, P<0.001). Benefit with apalutamide in rPFS was seen regardless of prior chemotherapy use or disease burden. Final analysis of OS showed apalutamide improved OS, reducing the risk of death by 35% (median OS for apalutamide not reached vs 52.2 months in the placebo group; HR, 0.65; 95% CI, 0.53 to 0.79; P < 0.0001)(37, 38). Benefit with apalutamide in rPFS and OS was seen regardless of disease burden and timing of metastases (de-novo vs metachronous).

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.

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

Abiraterone acetate plus prednisone in combination with docetaxel may be considered for patients with mCNPC/mCSPC with low volume disease *(Level of evidence 3, Weak recommendation).*

Recent data from the PEACE-1 trial showed the benefits of the combination of ADT plus prednisone plus docetaxel and abiraterone acetate compared to docetaxel and ADT.(39) In a 2 × 2 factorial design, patients with *de novo* metastatic castration sensitive prostate cancer (n = 1,173) were randomly assigned to receive standard of care (n = 296), standard of care plus abiraterone and prednisone (n = 29), standard of care plus radiotherapy (n = 293), or the standard of care plus abiraterone plus radiotherapy (n = 291). Standard of care treatments included ADT with or without docetaxel, and overall 60% of participants received a median of 6 cycles of docetaxel.

Compared with standard of care (SOC)(ADT plus docetaxel without abiraterone), the addition of abiraterone improved the median OS reduced the relative risk of death from any cause by 25% (adjusted HR for OS 0.75, 95·1% CI 0.59–0.95; p=0.017). Using CHAARTED study criteria, high volume patients 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); overall survival 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 low volume patients, 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.

Darolutamide in combination with ADT and 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 patients with mCSPC to receive docetaxel and androgen deprivation with (n=651) or without (n=655) darolutamide. (40) A significant improvement in

overall survival 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 4 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 and 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% and 9.2%).

The ARASENS and PEACE-1 trials both show the benefits of adding an androgen receptor pathway inhibitor (ARPi) to docetaxel in castration sensitive prostate cancer (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.

Both studies show in subgroup analyses that there are limited patient characteristics that may influence the use of triplet vs doublet therapy as benefits in OS and rPFS was seen in a majority of prespecified patient factors. One patient characteristic, tumor volume based on CHARRTED study criteria (7), 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 overall survival 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 regardless of stage of diagnosis. (40) 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.

PREVENTION OF OSTEOPOROSIS

All patients with mCNPC/mCSPC treated with ADT should be assessed for fracture risk. All patients treated with ADT require vitamin D supplementation (800-1200IU daily) and calcium supplementation (800mg-1000mg total intake daily). Those at high risk of fractures should be treated (zoledronic acid 5mg once a year, alendronate 70mg weekly, denosumab 60mg every 6 months).

Due to the evolution of combined therapy with ADT to treat mCNPC, the survival of patients with *de novo* PC is increasing and length of time bone is exposed to the effects of ADT is increasing. As such, these patients are at risk of significant bone loss and are at risk of osteoporosis and fragility fractures. Bone loss occurs quickly while on ADT and within one year patients can lose up to 10% of their bone mineral density (BMD)(41-43). Patients with mCNPC initiating ADT should have baseline BMD with dual-energy x-ray absorptiometry (DXA) as well

as utilization of fracture risk calculators such as FRAX(44). DXA should be performed at least every two years and more often in untreated patients at high risk or if there is a history of osteoporosis/osteopenia.

Patients with mCNPC/mCSPC treated with ADT should be encouraged to take vitamin D (1000IU daily) and total calcium intake of at 800mg-1000mg daily. Specific lifestyle changes including: smoking cessation, reduction in alcohol and caffeine intake and increase weight-bearing exercises. If DXA scanning shows any evidence of osteopenia (T-score of <-1 and > -2.5) or osteoporosis (T-score of less than -2.5) men should be started a bone targeted therapy to improve bone mineral density and reduce the risk of fragility fractures (zoledronic acid 5mg once a year, alendronate 70mg weekly, denosumab 60mg every 6 months)(42, 43, 45). Bone targeted therapy at these doses are much lower than those to prevent skeletal-related events (SREs) in patients with mCRPC and therefore, are associated with significantly reduced side effects; incidence of clinically significant hypocalcemia and osteonecrosis of the jaw is rare using denosumab or zoledronic acid with these lower doses. (46, 47)

TREATMENT OF OLIGO-METASTATIC DISEASE

There is evolving evidence of the role of radiation to asymptomatic distant metastases, especially in low burden "oligometastatic" disease. Currently, there is limited data to provide general recommendations, however, consideration in a multi-disciplinary setting would provide the best setting to determine optimal management consideration case-by-case and consideration for the ongoing clinical trials.

MULTIDISCIPLINARY CONSULTATION

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

Timing of initiation and choosing the optimal systemic therapy from a multitude of options requires careful consideration of multitude of 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.

CONCLUSIONS

The last 5 years has seen a significant growth of life-extending therapies for patients that has changed the landscape of treatment for mCNPC/mCSPC. All patients with mCNPC/mCSPC, regardless of disease volume and whether metastases were de-novo or metachronous, should be

offered treatment-intensifying systemic therapy in addition to ADT. For those with low risk/ low volume disease, radiation therapy to the prostate should be strongly considered in addition to systemic therapy.

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