CUBA-CUOG Guidelines for the Management of Castration Resistant Prostate Cancer (CRPC): 2013 Update

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**Definition of CRPC**

CRPC is defined by disease progression despite androgen depletion therapy (ADT) and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

Advanced prostate cancer has been known under a number of names over the years, including hormone resistant prostate cancer (HRPC) and androgen insensitive prostate cancer (AIPC). Most recently, the terms castration resistant prostate cancer or castration recurrent prostate cancer (CRPC) were introduced with the realization that extra testicular androgen production plays a significant role in the resistance of prostate cancer cells to medical or surgical castration therapy(1). In their second publication, the Prostate Cancer Working Group (PCWG2) defined CRPC as a continuum on the basis of whether metastases are detectable (clinically or by imaging) and whether the serum testosterone is in the castrate range by a surgical orchidectomy or medical therapy (2). This creates a clinical-states model where patients can be classified. The rising PSA states (castrate and non-castrate) signify that no detectable (measurable or non-measurable) disease has ever been found. The clinical
metastases states (castrate and non-castrate) signify that disease was detectable at some point in the past, regardless of whether it is detectable now.

Prognosis is associated with several factors, including performance status, presence of bone pain, extent of disease on bone scan, and serum lactate dehydrogenase and alkaline phosphatase levels. Bone metastases will occur in 90% of men with CRPC and can produce significant morbidity including pain, pathologic fractures, spinal cord compression, and bone marrow failure. Paraneoplastic effects are also common including anemia, weight loss, fatigue, hypercoagulability, and increased susceptibility to infection.

**CRPC presents a spectrum of disease ranging from patients without metastases or symptoms with rising PSA levels despite ADT, to patients with metastases and significant debilitation due to cancer symptoms.**

**MANAGEMENT OF CRPC**

**Secondary hormonal manipulations**

In patients who develop CRPC and who are asymptomatic or minimally symptomatic, secondary hormonal treatments may be attempted. (LEVEL 3, GRADE C)

To this date, no study of secondary hormone treatment has shown survival benefits but most trials have been smaller, were not designed to evaluate overall survival and heavily confounded by future treatments used. In patients treated with LHRH agonist/antagonist monotherapy or who have had an orchidectomy, addition of total androgen blockade (TAB) with androgen receptor antagonists such as bicalutamide can offer PSA responses in 30 to 35% of patients (3).

For patients who progress on ADT without evidence of distant metastases it is suggested to screen for bone metastases and monitor for visceral metastases/progression with imaging of the abdomen and chest. Exact timing of imaging may be modulated using PSA doubling time, with patients having a PSA doubling time of <6 months at particular risk for developing earlier metastases (4). Imaging techniques most commonly used include nuclear bone scans and abdominal CT and chest X-ray. The role of MRI and PET are still unclear.

**For patients who have undergone TAB, the antiandrogen should be discontinued to test for an antiandrogen withdrawal response (AAWD). Introduction or changes of an**
antiandrogen (AA) or the use of corticosteroids with or without ketoconazole have been reported to cause transient PSA reductions in approximately 30% of patients. (LEVEL 3 Grade C).

Because the androgen receptor remains active in most patients who have developed castration resistant disease, it is recommended by groups such as ASCO (American Society of Clinical Oncology), NCCN (National Comprehensive Cancer Network), CCO (Cancer Care Ontario) and others that ADT should be continued (LEVEL 3, GRADE C).

Novel agents that potently affect the androgen receptor signalling have recently been developed and have renewed the enthusiasm for effective hormone manipulation. Currently, in men with CRPC, phase 3 clinical trials evaluating whether prednisone and abiraterone acetate, a potent and irreversible inhibitor of CYP-17, a critical enzyme in androgen biosynthesis, can improve survival when compared to prednisone and placebo have been published (5-8). In the post docetaxel setting abiraterone/prednisone was shown to significantly prolong median overall survival compared to placebo/prednisone by 3.9 months 14.8 vs 10.9 months (HR = 0.64, p=0.0001). Abiraterone acetate was also shown to improve patient reported outcomes (pain, quality of life) and delay skeletal related events. In light of these positive results, abiraterone was approved by Health Canada for CRPC patients previously treated with docetaxel.

In patients progressing on or after docetaxel based chemotherapy abiraterone acetate (1000mg per day) plus prednisone (5mg BID) is a treatment option that should be offered. (LEVEL 1, Grade A)

In 2012 results of the AFFIRM study of enzalutamide (formerly MDV-3100, a potent inhibitor of the androgen receptor (26) vs. placebo in patients previously treated with docetaxel, were recently published by Scher and colleagues in the New England Journal of Medicine (27). The study demonstrated a significant overall survival advantage of 4.8 months (HR 0.62) with
improvements in pain, PSA and radiologic PFS. Enzalutamide has been approved for use by the US FDA and is under review by Health Canada as a treatment option for metastatic CRPC following docetaxel based chemotherapy.

At the 2012 ASCO Annual meeting, the results of a phase III study with abiraterone acetate in patients that were chemotherapy naïve was presented by Ryan et al. The study was unblinded at the second interim analysis due to a very significant improvement in radiographic progression free survival, and patients on the placebo arm crossed over to active therapy. The co-primary endpoint of overall survival showed a strong trend towards statistical significance. Other endpoints were an improvement in time to chemotherapy and opiate use. The results of this study have now been published (8) and the US FDA has recently expanded the use of abiraterone acetate to include patients that are chemotherapy naïve. This indication is under review by Health Canada at this time. The results of a similar trial with enzalutamide in chemotherapy-naïve CRPC patients are awaited (PREVAIL). The updated NCCN guidelines for 2013 have added both abiraterone and enzalutamide as first line therapeutic options for metastatic CRPC. Abiraterone and enzalutamide may be potential therapeutic options in patients who are deemed to be chemotherapy ineligible. As of now the use of these agents prior to docetaxel has not received health Canada approval and access may be limited depending on provincial reimbursement guidelines.

Systemic corticosteroid therapy

Corticosteroid therapy with low dose prednisone or dexamethasone may also offer improvements in PSA values and/or palliative outcomes in up to 30% of patients in both symptomatic and asymptomatic men. Steroids may also exert an anti-neoplastic effect on prostate cancer (9,10). (LEVEL 3, GRADE C)

First-Line Systemic Chemotherapy
Currently, only patients with CRPC who have detectable macroscopic metastatic disease should be considered for systemic chemotherapy outside of a clinical trial. Patients with advanced prostate cancer should be referred early for possible chemotherapy and should optimally receive multidisciplinary care to maximize survival and optimize quality of life. Because any treatment for advanced disease remains non-curative, patients with advanced prostate cancer should be encouraged to participate in clinical trials.

Tannock et al randomized 1006 patients to one of three treatment arms: docetaxel (75 mg/m2 intravenously every three weeks), docetaxel (30 mg/m2 five-times weekly for five of six weeks), or control therapy with mitoxantrone (11). The study reported improved survival with docetaxel (q3 week) compared with mitoxantrone-prednisone (median survival, 18.9 versus 16.5 months; hazard ratio [HR] = 0.76 [95% confidence interval (CI), 0.62–0.94], two-sided p = 0.009). No overall survival benefit was observed with docetaxel given on a weekly schedule (HR = 0.91, [95% CI, 0.75–1.11], two-sided p = 0.36). Significantly more patients treated with docetaxel (q3 week) achieved a pain response compared with patients receiving mitoxantrone (35% versus 22%, p = 0.01). QoL response defined as a sustained 16-point or greater improvement from baseline on two consecutive measurements was higher with docetaxel given every three weeks (22% versus 13%, p = 0.009) or weekly (23% versus 13%, p = 0.005) compared with mitoxantrone. PSA response rates were also statistically significantly higher with docetaxel compared to mitoxantrone. Twenty-seven per cent (n = 412) and 29% (n = 196) of patients in the two trials had measurable disease.

Based on the results of randomized controlled trials, it is recommended that for men with metastatic CRPC and clinical or biochemical evidence of progression, treatment with docetaxel 75 mg/m2 administered intravenously every three weeks with 5mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation, and quality of life (11,12). (LEVEL 1, Grade A)
Although patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted, the duration of therapy should be based on the assessment of benefit and toxicities. Rising PSA only should NOT be used as the sole criteria for progression and assessment of response should incorporate clinical and radiographic criteria. Alternative therapies that have not demonstrated improvement in overall survival but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone (LEVEL 2, GRADE B).

The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients and individualized based on their clinical status and preferences. (LEVEL 3, GRADE C)

Use of estramustine in combination with other cytotoxic agents is not recommended due to the increased risk of clinically important toxicities without evidence of improved survival or palliation. (LEVEL 2, GRADE C)

For patients who do not respond to first line ADT or progress clinically or radiologically without significant PSA elevations may have neuroendocrine differentiation. Biopsy of accessible lesions should be considered to identify these patients who should then be treated with combination chemotherapy such as cisplatin/etoposide or carboplatin/etoposide. (LEVEL 3, GRADE C)

**Second-Line Systemic Chemotherapy**

Until recently mitoxantrone was considered de facto second line chemotherapy but has limited activity and increased toxicity in this setting. (LEVEL 4, GRADE D)

For patients who have not demonstrated definitive evidence of resistance to docetaxel, re-treatment with docetaxel can be considered (14-16) (LEVEL 3, GRADE C).
Recently reported results using cabazitaxel compared to mitoxantrone in patients previously treated with docetaxel has shown a statistically significant survival advantage (17). This randomized, placebo-controlled trial recruited 755 docetaxel-pretreated CRPC patients. OS was the primary endpoint of the study. Patients were randomized to receive prednisone 10 mg/day with 3-weekly mitoxantrone 12 mg/m² or cabazitaxel 25 mg/m². An advantage in survival emerged in favour of the cabazitaxel group, with a median survival of 15.1 months compared with 12.7 months in the mitoxantrone group (HR 0.70; 95% CI 0.59, 0.83; p<0.0001).

In light of these positive results, cabazitaxel is considered a therapeutic option for metastatic CRPC patients progressing on or following docetaxel. (LEVEL 1, GRADE A)

Palliative Radiation

Bone metastases from prostate cancer are often radiosensitive and most men will experience partial or complete pain relief from external beam radiation to a specific lesion. Studies have shown that a single fraction is as effective as five fractions in providing palliation. However, more patients require retreatment for pain recurrence with single fraction radiation. (LEVEL 2, GRADE B)

Radionuclide therapy in the form of systemic strontium-89 therapy may be useful in the palliation of CRPC when multiple skeletal sites are involved in carefully selected patients. Risks include severe prolonged myelosuppression and transfusion dependence. Strontium-89 may be associated with a worse overall survival as compared to external beam radiotherapy. (34,35)

Bone-targeted Therapy

Bone loss associated with ADT has been shown to increase the risk of fracture (18-22). Moreover, approximately 90% of patients with metastatic CRPC will develop bone metastases, which cause local decreases in bone integrity. Patients are at significant risk of skeletal
complications that include pathological fractures, debilitating bone pain requiring palliative radiation therapy, and spinal cord compression. QoL is affected by these complications.

In men with castration-resistant prostate cancer and bone metastases, zoledronic acid (4mg IV) or denosumab (120mg S/C) every 4 weeks is recommended to prevent disease related skeletal complication including pathological fractures, spinal cord compression, surgery or radiation therapy to bone (23,24) (LEVEL 1, GRADE A).

Bisphosphonates other than zoledronic acid are not known to be effective for the prevention of disease-related skeletal complications. Serum creatinine monitoring is suggested prior to each dose of zoledronic acid. Results from the randomized study showed fewer men receiving zoledronic acid had skeletal-related events while on study than men in the placebo group (38% versus 49% P=0.02) (23). Zoledronic acid also increased the median time to first skeletal-related event (SRE) (488 days versus 321 days P=0.01). There was an overall 36% reduction in the rate of SRE’s in treated patients. Zoledronic acid should be initiated at reduced dose in men with impaired renal function (estimated creatinine clearance 30-60 ml/min). Treatment is not recommended for men with baseline creatinine clearance <30 ml/min. Based on recommendations for other settings bisphosphonate therapy for bone metastases should be continued for as long as clinically beneficial. The optimal duration of zoledronic acid in men with castration-recurrent prostate cancer and bone metastases is undefined however efficacy and safety for up to 24 months was shown.

Other bone-targeted agents include denosumab, a fully humanized monoclonal antibody against RANK ligand, which has been shown to be effective in preventing bone loss and new vertebral fractures due to ADT (22). In the setting of metastatic CRPC, denosumab (120mg SC every 4 weeks) compared to zoledronic acid (4mg IV every 4 weeks) has shown significant improvement of the time to the first SRE (20.7 vs 17.1 months; P< 0.001 for non-inferiority; P= 0.008 for superiority) while overall survival and progression free survival were not different (24). Hypocalcemia was more common in the denosumab arm (13%) than the zoledronic acid arm (6%) (P< 0.0001) and a non-significant trend toward higher osteonecrosis of the jaw was seen in the denosumab arm (2.3% vs 1.3%; P= 0.09). No dose modification for renal function
is necessary in the case of denosumab, however the risk of hypocalcaemia is increased and calcium monitoring and supplementation is recommended for both denosumab and zoledronic acid.

Zoledronic acid and denosumab are associated with 1-2% risk of osteonecrosis of the jaw (ONJ) (24). Most but not all patients who develop ONJ have pre-existing dental problems. **Good oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce risk of ONJ (28-30) (LEVEL 3, GRADE C).** Zoledronic acid and Denosumab have been used safely with a variety of cytotoxic chemotherapies in clinical trials (23,24).

In a recent placebo controlled trial denosumab significantly increased the bone-metastasis-free survival in patients with non-metastatic CRPC by a median of 4.2 months compared with placebo (29.5 vs 25.2 months; HR, 0.85; 95% CI, 0.73-0.98; P=0.028) (25). **Denosumab is not approved for bone metastases prevention by Health Canada and the US FDA has rejected the use of denosumab for this indication.**

**Future potential therapies**

A recently completed phase III study of patients with metastatic CRPC were randomized on a 2:1 basis to either radium-223 chloride (an alpha emitting calcium mimic which preferentially targets bone metastases) or placebo. Overall survival was the primary endpoint. Median survival was 14 months for the treated patients as opposed to 11.2 months for those who received a placebo, conferring an approximate 30% improvement in OS (HR 0.699, p 0.0022). This is still unpublished and was presented at ASCO GU in 2012 by Parker et al.(36)

**Conclusion**

Advances in treatment for men with CRPC have improved survival and QOL but most, if not all, eventually succumb from their disease and better treatments are required.
Several new agents are being studied in a pre-chemotherapy setting, in combination with docetaxel as well as in the post docetaxel setting (27-33). It is hoped that the near future will lead to more therapeutic options for patients with CRPC. Because CRPC remains an incurable and ultimately fatal illness, inclusion of patients in clinical trials at all stages of the disease remains paramount.

Summary

For patients with metastatic CRPC, docetaxel based chemotherapy is recommended to improve survival and quality of life. In addition, bone-targeted agents should be used to reduce the risk of skeletal-related complications. Post docetaxel therapeutic options with proven survival advantages are now available in Canada. Other treatments have reported positive results or are presently under investigation and may soon add to the available therapeutic options in Canada.
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*pending health Canada approval


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