

Guidelines for the Management of Castrate Resistant Prostate Cancer (CRPC)

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Conflict of interest Declaration:

FS, SJH serve as advisors and have conducted research with Novartis, Sanofi Aventis, and Amgen.

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Levels of evidence and grades of recommendation employing the International Consultation on Urologic Disease (ICUD)/WHO modified Oxford Center for Evidence-Based Medicine grading system

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 castrate resistant prostate cancer or castration recurrent prostate cancer (CRPC) were introduced with the realization that intracrine/paracrine androgen production plays a significant in the resistant of prostate cancer cells to testosterone suppression 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 noncastrate) signify that no detectable (measurable or non-measurable) disease has ever been found. The clinical metastases states (castrate and noncastrate) 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 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 relatively asymptomatic, secondary hormonal treatments may be attempted. (LEVEL 3, GRADE C)

To this date, no study of secondary hormone treatment has shown benefits in terms of survival but most trials have been smaller and heavily confounded by future treatments used. In patients treated with LHRH agonist monotherapy or who have had an orchidectomy, total androgen blockade (TAB) with testosterone antagonists such as bicalutamide can offer PSA responses in 30 to 35% of patients. For patients who progress on ADT without evidence of distant metastases it is suggested to screening 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. 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 could be discontinued to exclude an antiandrogen withdrawal response (AAWD). Introduction or changes of an AA or the use of Ketoconazole have been reported to have transient PSA reductions in approximately 30% of patients (3). (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).

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 (4, 5). (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 palliative, patients with advanced prostate cancer should be encouraged to participate in clinical trials.

Docetaxel and prednisone in combination are currently considered the standard of care for men with CRPC with detectable metastatic disease based largely on the simultaneous publication of two large randomized controlled trials comparing this combination to the previously established standard of mitoxantrone and prednisone (6,7) (LEVEL 1, GRADE A).

Docetaxel is a taxane drug that induces polymerization of microtubules and phosphorylation of bcl-2 protein. 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 (6). All patients also received prednisone 5mg po BID. Petrylak et al reported on 666 eligible patients randomized to docetaxel and estramustine (EMP) or mitoxantrone-prednisone(7). In addition to dexamethasone premedication, patients in the docetaxel arm also received warfarin and/or acetylsalicylic acid (ASA) as thrombosis prophylaxis during the course of the trial. Men in both trials had clinical evidence of metastases with or without symptoms and had undergone AAWD. Overall survival was the primary endpoint in both trials.

Tannock et al 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). Petrylak et al reported longer survival time with docetaxel-EMP combination chemotherapy compared with mitoxantrone (median survival, 17.5 versus 15.6 months; HR = 0.80 [95% CI, 0.67–0.97], two-sided p = 0.02). This trial also reported a median progression-free interval of 6.3 versus 3.2 months (HR = 0.73 [95% CI, 0.63–0.86], two-sided p < 0.0001) favouring docetaxel-EMP compared with mitoxantrone. Pain response was assessed in both trials. Significantly more patients treated with docetaxel (q3 week) achieved a pain response compared with patients receiving mitoxantrone (35% versus 22%, p = 0.01). A trend towards improved pain response was observed with weekly docetaxel versus mitoxantrone (31% versus 22%, p = 0.08). 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. Petrylak et al reported no difference in patient reported pain relief between arms in their trial and did not assess QoL. In both trials, 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. Objective response rates for docetaxel (q3 weeks) and mitoxantrone were 12% versus 7%, respectively. Petrylak reported objective response rates of 17% and 11% favouring docetaxel-EMP compared with mitoxantrone. The differences in objective response rates between arms were not statistically significant in either trial.

Based on the results of these two randomized controlled trials, it is now recommended that for men with clinical or biochemical evidence of progression and evidence of metastases, 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 (8,9). (LEVEL 1, Grade A)

Although in the two pivotal trials, 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 (10). **(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. The NCCN guideline suggests that 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

Unfortunately, no treatment has been shown to improve survival or quality of life in patients who have progressed on or soon after docetaxel-based chemotherapy and participation to a clinical trial should be encouraged (11-15).

For now mitoxantrone is 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 agent can be considered (16-19) (LEVEL 3, GRADE C).

Recently reported unpublished results using cabazitaxel compared to mitoxantrone in patients previously treated with docetaxel has shown a statistically significant survival advantage (20). 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 may soon play a prominent role as second-line treatment in CRPC patients.

Palliative Radiation

Bone metastases from prostate cancer are often radiosensitive and most men will experience partial or complete pain relief from radiation to a specific lesion (21). Studies have shown that a single fraction is as effective as five fractions in providing palliation. However, more patients require retreatment for pain recurrence. (LEVEL 2, GRADE B)

In some patients with diffuse bone pain, radio-isotopes can be considered. Because of their potential for marrow suppression, adequate blood counts are required in order to initiate treatment. The two main radio-isotopes used are strontium and samarium. The main advantage of samarium over strontium is its shorter scatter which causes less marrow suppression. (LEVEL 3, GRADE C)

Bone-targeted Therapy

Bone loss associated with ADT has been shown to increase the risk of fracture (22-24). Moreover, approximately 90% of patients with metastatic CRPC will develop bone metastases, which cause local decreases in bone integrity. Patients are significant risk of skeletal complications, including pathological fractures, debilitating bone pain and spinal cord compression. The patient's QoL is affected by these complications (25).

In men with castration-recurrent prostate cancer and bone metastases, zoledronic acid (4mg IV) every 3-4 weeks is recommended to prevent disease related skeletal complication including pathological fractures, spinal cord compression, surgery or radiation therapy to bone (26,27) (LEVEL 1, GRADE A).

Other bisphosphonates are not known to be effective for the prevention of disease-related skeletal complications. The infusion time for zoledronic acid should be no less than 15 minutes to reduce the risk of affecting renal function. Serum creatinine monitoring is suggested prior to each dose. 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% $P=0.02$). Zoledronic acid also increased the median time to first skeletal-related event (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 has been shown in the RCT. Zoledronic acid and other bisphosphonates are associated with increased risk of osteonecrosis of the jaw (ONJ). 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 has been used safely with a variety of cytotoxic chemotherapies in clinical trials (31). Adverse events reported during bisphosphonate treatment did not appear to increase with concomitant chemotherapy.

Based on the available evidence, several guidelines, including those of the National Comprehensive Cancer Network (NCCN), the European Association of Urology and the International Consultation on Urological Diseases, recommend that bisphosphonates be used to preserve bone health and to prevent skeletal complications in patients with bone metastases from CRPC, whether asymptomatic or symptomatic. Other bone-targeted agents include the RANK ligand inhibitor denosumab, which has been shown to be effective in preventing bone loss and new vertebral fractures due to ADT (32, 33). Denosumab has recently reported the results of a RCT showing effectiveness in delaying and reducing SRE's when compared to zoledronic acid and may soon become another option for patients with metastatic CRPC (34).

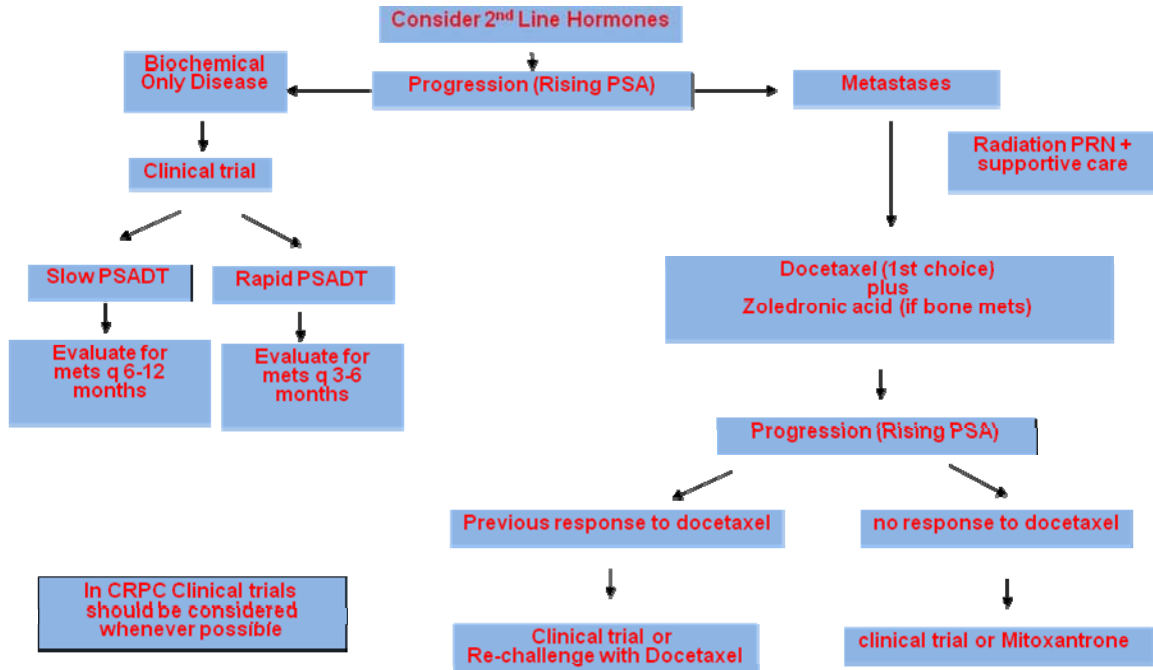
Clinical trials and future directions

Men with CRPC are living longer and with improved 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. 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, participation to clinical trials at all stages of the disease remains paramount.

Summary

Advanced CRPC is a multifaceted problem and needs a multidisciplinary approach. Maintenance of quality of life and supportive care remains the priority. For patients with metastatic CRPC docetaxel based chemotherapy is recommended to improve survival and quality of life. Also recommended is zoledronic acid to reduce the risk of bone complications. There are other treatments presently under investigation that may soon add to the therapeutic options available. Building on what is presently available is necessary to further improve the outcome in these poor-prognosis patients.

Proposed approach for patients with Castrate Resistant Prostate Cancer with presently available agents



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