Secondary hormonal manipulation in castration resistant prostate cancer

Sohaib Al-Asaaed, MD, Eric Winquist, MD
London Health Sciences Centre and Western University, London, Ontario, Canada

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Introduction: *Castration resistant prostate cancer (CRPC) is the single common pathway to prostate cancer death. For men with symptomatic metastatic disease, docetaxel chemotherapy remains a standard of care. However, blood prostatic-specific antigen (PSA) testing allows the identification of CRPC before clinical metastases or symptoms occur, providing a long diagnostic lead time in many patients. The use of secondary hormonal manipulations (SHMs) in men not candidates for immediate chemotherapy is reviewed.*
Materials and methods: *PubMed was searched for randomized clinical trials, systematic reviews or clinical practice guidelines addressing SHMs in CRPC.*
Results: *A recent systematic review and practice guideline was identified, and used as the evidence base for this review along with reports from randomized trials over the past year.*
Conclusions: *The goals of therapy with SHMs should be discussed with patients and their preferences considered. In men without clinical evidence of metastases, gonadal androgen suppression should be maintained and generally patients should be observed. There is no clear evidence that SHMs are of benefit in these patients. Abiraterone plus prednisone is of proven benefit in men with CRPC metastases who are without significant symptoms prior to chemotherapy. Based on emerging data, enzalutamide may be of similar benefit. Use of other SHMs should be based on patient preference and consideration of possible adverse effects; with the exception of low dose prednisone, there is little evidence of benefit supporting their use. For patients accepting these uncertainties, a trial of nonsteroidal antiandrogen may be considered as an adjunct to observation, followed by low dose corticosteroid with immediate or delayed addition of abiraterone (in men with metastases) as a reasonable next step.*

Key Words: enzalutamide, hormone-dependent, prostatic neoplasms, castration resistant, abiraterone, drug therapy

Introduction

Men with castration resistant prostate cancer (CRPC) and clinically significant metastatic disease (rapid disease progression, persistent and worsening symptoms, or visceral metastases) should be assessed for palliative chemotherapy, which remains a standard of care, with docetaxel currently the agent of choice.[1,2] The diagnosis of CRPC is made when there is evidence of disease progression (biochemically, radiographically and/or symptomatically) in the presence of castrate levels of testosterone (< 50 ng/mL or < 1.7 nmol/L).[3]

Address correspondence to Dr. Eric Winquist, London Health Sciences Centre, 790 Commissioners Road East, London, ON N6A 4L6 Canada

There is no clear temporal relationship between the onset of metastatic disease and the development of CRPC, though biochemical recurrence characterized by an increasing blood prostatic-specific antigen (PSA) level alone is usually the first evidence of CRPC.[4-6] Thus the emergence of CRPC is often characterized by a lengthy "lead time" during which men without clinical evidence of metastases are observed to have rising PSA levels.

CRPC is a heterogeneous disease and consists of a spectrum of clinical states. When considering use of secondary hormonal manipulations (SHMs) it is useful to consider patients in three clinically-defined groups: 1) those with biochemical recurrence alone without any evidence of metastases, 2) those with evidence of metastatic disease and minimal or no symptoms,

and 3) those with metastases and significant cancer symptoms (who are usually candidates for palliative chemotherapy or potentially radium 223).[7] As CRPC is incurable the focus of therapy should be on optimizing a patient's quality and quantity of life, and judicious and timely use of suitable agents available in this "pre-chemotherapy" phase is important, and is the topic of this review. These goals of therapy should be discussed with the patient, and an understanding of the patient's values is essential in creating a strategy for how aggressively or conservatively they wish to pursue active therapeutics. Counseling patients about the interpretation of PSA values which may fluctuate and be misleading in CRPC, and emphasizing the goal of optimal quality of life is recommended.

Prior to considering SHMs, the question of maintaining castrative therapy may be raised. A multivariate analysis by Taylor et al[8] identified prognostic factors associated with worse survival in men with CRPC including: poor performance status (non-ambulatory), soft-tissue visceral involvement, age > 65 years-old, recent weight loss of > 5%, and discontinuation of endocrine therapy. Inadequate gonadal androgen suppression (androgen deprivation therapy—ADT) has also been associated with resistance to anticancer treatment, presumably due to anti-apoptotic effects of androgens in prostate cancer cells.[9] There is some evidence that intermittent ADT may improve side effects and result in cost savings in CRPC.[10] However, it remains the current standard of care to maintain all men with CRPC on continuous gonadal androgen suppression with luteinizing hormone releasing hormone (LHRH) agonist or antagonist if they have not been treated with bilateral orchidectomy, although these agents may be discontinued as patients near their end-of-life.[11,12]

Why use secondary hormonal manipulation in the era of newer agents?

New hormonal agents have emerged over the past 5 years and been approved for the treatment of CRPC, and are currently being studied earlier in the natural history of CRPC. This raises questions about the optimal use of these agents, and has prompted the development of clinical practice guidelines. The American Urological Association has recently published a guideline for CRPC, and the systematic review supporting this guideline provides the evidence base for this review of SHMs.[13] Men presenting with or who develop clinically significant metastatic CRPC during SHMs should be assessed for palliative chemotherapy, and may need to proceed to chemotherapy without further SHMs. In men without evidence of CRPC metastases there is no evidence available from randomized controlled trials that SHMs ultimately improve important disease outcomes, and so the risk-benefit of interventions should be considered from the view that they may merely manipulate PSA levels without other proven benefits.[13] The natural history of CRPC without metastases was studied in men enrolled in the placebo group of an aborted trial of zoledronic acid versus placebo reported by Smith et al.[14] A third of patients developed bone metastases at 2 years. Median bone metastasis free survival was 30 months, though time to first bone metastasis and overall survival were not reached. An elevated baseline PSA (> 10 ng/mL) and rapid PSA velocity (< 6 months) independently predicted shorter time to bone metastasis, metastasis free survival, and overall survival. Careful observation or offering clinical trial participation to CRPC patients without metastases may be considered reasonable standards of care.[13,15] Currently there is no high level evidence supporting the use of either SHMs or newer agents such as abiraterone or enzalutamide in CRPC patients without metastases, and clinical trials studying these are underway. In men with relatively stable asymptomatic or minimally symptomatic non-visceral metastatic disease, the use of abiraterone-prednisone may also be considered.[16] Men with bone metastases should also be considered for bone protective therapy as prophylaxis for skeletal-related events.[17]

Agents and applications

There is not sufficient data and no clinical consensus supporting an optimal sequencing of SHMs in men with early CRPC, so practical considerations including patient preferences and drug availability usually dictate treatment options. Switch to an alternate SHM should be considered if toxicity or evidence of disease progression occurs, but otherwise observation on treatment is usually continued without interruption. As mentioned ADT should be continued despite evidence of CRPC and serum testosterone level should be confirmed within the castrate range; if it is not, then a switch of LHRH agonist/antagonist or bilateral orchidectomy should be considered. A therapeutic trial of a non-steroidal antiandrogen (NSAA) is routine when biochemical evidence of CRPC is first observed on ADT monotherapy, but there is no clear evidence that this improves quality or quantity of life.[13] Generically available NSAAs include bicalutamide, flutamide and nilutamide. Although no studies have investigated optimal dosing, bicalutamide 50 mg PO

daily is often used as it is convenient and appears to have the best side effect profile in this class.[18]

The response rate to first generation antiandrogens is expected to be approximately 15%.[19,20] Switching to other NSAA such as flutamide or nilutamide has been proposed but is associated with a low and idiosyncratic response rate and the potential for exposing patients to a greater risk of adverse effects.[21] Two new agents, enzalutamide and ARN-509, are very potent antiandrogens referred to as "androgen receptor signaling inhibitors".[3,22] They not only potently bind to the androgen receptor, but also interfere with its translocation into the nucleus and with gene transcription. Both are currently under study in clinical trials as SHM in men with CRPC with and without metastases.

Some SHM agents of historical interest include estrogens (eg. diethylstilbestrol); the steroidal antiandrogen, cyproterone acetate; and the steroidal progestational drug, megestrol acetate. Diethylstilbestrol (a synthetic non-steroidal estrogen) may induce responses in CRPC and does not induce tumor flare or vasomotor hot flashes but is associated with high cardiovascular and thromboembolic complication rates and has been largely abandoned.[23,24] Evidence for the value of other estrogen formulations in CRPC is sparse. Megestrol acetate was investigated by Dawson et al[25] as a SHM in men with CRPC but demonstrated a low response rate of 14% (objective and PSA decline rates) and no dose response with higher doses was observed. Cyproterone has also been associated with PSA response in men with CRPC; however, both megestrol and cyproterone have been associated with an increased risk of cardiovascular side effects, and have generally been abandoned in practice.[26]

The phenomenon of biochemical and clinical response to discontinuation of antiandrogen ("antiandrogen withdrawal"--AAWD) has also been observed with a number of other SHM agents.[27,28] This is postulated to be due to a change in androgen receptor function in response to chronic antiandrogen therapy, with paradoxical stimulation of the androgen receptor due to receptor mutation.[29] The median antiandrogen withdrawal response duration is approximately 4-6 months.[30] If clinically appropriate for the patient, assessment for antiandrogen withdrawal response is generally recommended particularly in patients treated with NSAA for a long duration. Patients who undergo AAWD from bicalutamide should be observed for up to 8 weeks owing to this drug's longer half-life.

Currently after NSAA and AAWD, a next reasonable step is a trial of low corticosteroid with or without ketoconazole or abiraterone. Interestingly, prednisone 5 mg twice daily was associated with a PSA response rate of 24%, median PSA progression-free survival of 5.6 months, and objective response rate of 16% in a recently reported blinded placebo-controlled trial.[16] Abiraterone acetate may be considered at this juncture in suitable patients with metastatic disease, but is expensive, may not be funded or available for this indication in all jurisdictions, and is associated with incremental mineralocorticoid side effects.[16] In view of this, initiation of low dose prednisone alone with the addition of abiraterone at progression in these patients is also quite a reasonable strategy.

Historically, bilateral adrenalectomy to eliminate adrenal androgens as a method of SHM was superseded by use of aminoglutethemide and the imidazole antifungal agent, ketoconazole. The activity of ketoconazole in prostate cancer is thought to be due to inhibition of the cytochrome p450 enzymes CYP3A4 and CYP17 in the gonad and adrenal gland, with possible additional effects due to androgen receptor antagonism.[31] In a randomized trial of men with CRPC, 27% of those receiving ketoconazole 400 mg PO tid, hydrocortisone and AAWD had a PSA response, and the objective response rate was 20%.[32] Ketoconazole 200 mg PO tid was noted to elicit a comparable PSA response rate in a single arm study.[33] However, PSA response to ketoconazole should be interpreted with caution as it is confounded by use of low dose corticosteroids; low dose prednisone had similar PSA and objective response rates in the control arm of a recent randomized trial.[16] Ketoconazole may be cautiously considered as an alternative in patients who cannot afford or access abiraterone; however, ketoconazole has been banned for systemic use in the European Union due to serious hepatic toxicity, and pretreatment with ketoconazole may reduce the efficacy of abiraterone.[34,35]

Despite its limitations, ketoconazole provided inspiration for pursuing the inhibition of steroidogenesis as an additional therapeutic strategy in CRPC. At the forefront of this approach is abiraterone acetate which potently inhibits CYP17 mediated steroidogenesis in the testicle, adrenal, and in intra- and peritumoral tissues resulting in undetectable androgen levels.[36] ADT should be continued with abiraterone, and low dose prednisone is given to suppress ACTH production and mitigate the mineralocorticoid adverse effects due to accumulated steroid precursors due to CYP17 blockade. Ryan et al[16] compared abiraterone acetate 1000 mg PO daily plus prednisone 10 mg PO daily to placebo plus prednisone in mainly asymptomatic chemotherapy-naive men with metastatic CRPC. A significant improvement in

radiographic progression-free survival was observed with abiraterone (16.5 versus 8.3 months; hazard ratio: 0.53 [95% confidence interval, 0.45-0.62], $p < 0.001$), and this was concordant with improvements in multiple other clinically relevant secondary endpoints including median times to opiate use for cancer-related pain, initiation of cytotoxic chemotherapy, decline in ECOG performance score by ≥ 1 point, and PSA progression. There was a trend to improvement in overall survival (hazard ratio: 0.75) that was not statistically proven. The toxicity profile associated with abiraterone appeared very acceptable, with a low rate of grade 3 or 4 adverse events and similar rates of cardiac disorders. Mainly grade 1 or 2 adverse effects due to mineralocorticoid-related toxic effects were more common in the abiraterone-prednisone group than in the prednisone-alone group, including hypertension (22% versus 13%), hypokalemia (17% versus 13%), and fluid retention or edema (28% versus 24%). Abiraterone has been approved by the United States Food and Drug Aadministration and Health Canada, for use in men with metastatic CRPC before or after progression on docetaxel chemotherapy. A recent announcement of results from a large randomized trial indicated that enzalutamide may have similar benefits to abiraterone in this population, and presentation and publication of these data is awaited.[37]

Conclusions

SHMs in men with CRPC should consider the presence or absence of metastases, symptoms, and visceral disease; as well as patient preferences and available therapies. Maintenance of a castrate state is essential, and trials of SHMs may be considered if clinically reasonable but should not delay use of palliative chemotherapy if need becomes evident. For men without metastases, observation or clinical trial participation should be considered the standard of care. For men with metastases and minimal or no symptoms, abiraterone plus prednisone has clearly established benefit in quality and probably quantity or life given prior to chemotherapy compared to prednisone alone. Enzalutamide may provide similar benefits in this setting; high quality data is merging at the time of this report. The optimal choice or sequence of these two drugs is uncertain and will fuel future debate. The data supporting the use of other SHMs is very limited, and based more in convention than data. Taking a view, mindful of toxicity, that there may be value of these as an addition to a strategy of observation; serial therapy starting with a NSAA, with switch to low dose corticosteroid (with or without abiraterone acetate in men with metastases) in the absence of AAWD response is a reasonable approach. For other SHMs the evidence of benefit is sparse and their use cannot be recommended.

Disclosure

The authors have no potential conflict of interest. □

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