

# Management of castration-resistant (advanced) prostate cancer (CRPC): rationale, progress and future directions

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## Background

Prostate cancer is the most common solid organ cancer and the second most common cause of cancer-related deaths in Australian men.

## Objective

The aim of our review is to provide general practitioners with up-to-date information about castration resistance and hormonal dependence in prostate cancer. We summarise the current ongoing and completed clinical trials targeting hormonal pathways in metastatic prostate cancer.

## Discussion

The treatment paradigm of metastatic castration-resistant prostate cancer has changed markedly in the past decade and new agents targeting androgen receptor pathways have been introduced. However, the biggest challenge for clinicians is to develop guidelines to integrate these agents into clinical practice.

Prostate cancer is the most common solid organ cancer and the second most common cause of cancer-related deaths in Australian men. Recent statistics confirm that there are close to 20,000 diagnosed cases and more than 3300 deaths annually.<sup>1</sup> Since the 1940s, hormonal manipulation has been the mainstay of first-line treatment for metastatic prostate cancer.<sup>2</sup> Unfortunately, this approach is not curative and resistance inevitably arises. A conceptual shift in the understanding of prostate cancer has occurred recently, as it became apparent that castration resistance (that is, when systemic testosterone is measured below castrate levels) does not necessarily imply hormonal resistance altogether, and that further hormonal manipulation can result in ongoing biochemical, clinical and radiological responses.<sup>3</sup> Patients are generally stratified into two groups when they show signs of progression or castration-resistant prostate cancer (CRPC): those with biochemical recurrence (rising prostate-specific antigen [PSA]) and no radiological evidence of metastatic disease, and those with bony/visceral metastases (metastatic CRPC or mCRPC). Men in the latter category (mCRPC) could be either asymptomatic

or have symptomatic disease, thus prompting consideration of chemotherapy. This paper addresses interventions for patients with mCRPC.

The aim of our review is to provide general practitioners (GPs) with up-to-date information about castration resistance and hormonal dependence in prostate cancer. We aim to summarise the current ongoing and completed clinical trials that are targeting hormonal pathways in metastatic prostate cancer. This is an important area, as the number of men with advanced prostate cancer is increasing and we believe that GPs have a very important role in not only counselling patients about the new treatments but also rationalising the options on an individualised basis, with due consideration to the side effect profile, cost of the new treatments and quality-of-life outcomes.

## Literature search

The literature search was designed to identify relevant studies published between February 2004 and February 2013 in MEDLINE and EMBASE. The Cochrane Library was searched for systematic reviews and technology assessments. The literature search

combined the terms meta-analyses, systematic reviews, practice guidelines and RCTs with terms describing castration-resistant prostate cancer and systemic therapy interventions.

## Treatment options

### Hormonal treatment

Treatment of prostate cancer with intermittent androgen deprivation (IAD) versus continuous androgen deprivation (CAD) is a very widely debated topic. The results of a recent systematic review<sup>4</sup> showed overall survival to be similar for IAD and CAD in patients with locally advanced, recurrent or metastatic, hormone-sensitive prostate cancer. Impact on quality of life (QoL) was similar for both groups; however, sexual activity scores were higher and the incidence of hot flushes was lower in patients treated with IAD. There was no significant difference in timing to CRPC in either group.

There is increasing evidence that androgen receptor activity is consistently present in almost all patients who develop castration-resistant disease. Prostate cancer growth is stimulated initially by circulating testicular androgens. After treatment by medical or surgical castration, prostate cancers adapt to the androgen-deprived environment to maximise androgen receptor function

through mechanisms facilitated by the genetic instability of cancer cells.<sup>5–9</sup> In terms of second-line hormonal manipulations, no study to date has shown definite survival benefits.

In patients treated with luteinising-hormone-releasing hormone (LHRH) agonist monotherapy or in those who are surgically castrated, addition of an antiandrogen, such as bicalutamide, is recommended. That approach can produce a PSA response in approximately one-third of patients. For patients who are already receiving maximal androgen blockade and are showing signs of progression, the antiandrogen should be discontinued, which may result in an antiandrogen withdrawal response. The molecular mechanisms of this phenomenon are still unclear because of the lack of suitable experimental models. Other options may include a change to a different antiandrogen, to steroids or to ketoconazole.<sup>8,9</sup> Transient PSA reductions have been reported in 20–30% of patients with all of those modalities.

### First-line systemic chemotherapy

Docetaxel and prednisolone are currently considered the standard of care for men with CRPC and radiologically proven metastatic disease. This combination was recommended following publication of two large randomised controlled trials,<sup>10–12</sup> which compared it with the

previously used standard of mitoxantrone and prednisolone. The mean survival rates have been shown to be significantly better with docetaxel and prednisolone, compared with mitoxantrone and prednisolone.

Pain response was assessed in both the trials. The results showed significantly more patients treated with docetaxel achieved a pain response than with mitoxantrone (35% versus 22% with mitoxantrone,  $P = 0.01$ ). In both trials, PSA response rates were also statistically significantly higher with docetaxel than with mitoxantrone. In Australia, docetaxel is currently administered by oncologists and is given as inpatient chemotherapy.

### Second-line systemic chemotherapy

To date, two published trials (SPARC and TROPIC) have evaluated chemotherapeutic agents in patients with progressive disease after docetaxel.<sup>13,14</sup> The results showed statistically significant and clinically relevant survival advantage with cabazitaxel therapy. In light of these positive results, cabazitaxel was approved as a second-line chemotherapy drug in patients with CRPC and is available on the Pharmaceutical Benefits Scheme (PBS).

### Novel therapies (hypercastration)

Novel agents that have potent effects on the androgen axis and produce a hypercastration state have been developed recently, renewing interest in effective hormone manipulation. Recently, phase III clinical trials in men with CRPC have completed accrual. These trials have evaluated whether, compared with prednisolone and placebo, prednisone and abiraterone acetate can improve survival. Abiraterone acetate is a potent and irreversible inhibitor of CYP17, which is a critical enzyme in androgen biosynthesis.<sup>15,16</sup>

In the post-docetaxel setting, the combination of abiraterone and prednisone (compared with placebo and prednisone) was shown to significantly prolong median overall survival. In view of

**Table 1. Side effects and cost of treatment for second-line drugs for CRPC**

| Drug         | Adverse reactions  | Cost of treatment                | Eligibility criteria         |
|--------------|--|----------------------------------|------------------------------|
| Abiraterone  | <ul style="list-style-type: none"> <li>• Hypertension</li> <li>• Hypokalaemia</li> <li>• Fluid retention</li> <li>• Vomiting and diarrhoea</li> </ul>        | \$6000 (PBS)                     | Post-docetaxel CRPC          |
| Cabazitaxel  | <ul style="list-style-type: none"> <li>• Severe neutropaenia</li> <li>• Peripheral neuropathy</li> <li>• Nausea and vomiting</li> <li>• Diarrhoea</li> </ul> | \$5900 for five injections (PBS) | Post-docetaxel CRPC          |
| Enzalutimide | <ul style="list-style-type: none"> <li>• Hypertension</li> <li>• Anxiety</li> <li>• Fatigue</li> <li>• Seizures</li> </ul>                                   | Not approved in Australia        | Available in clinical trials |

these results, abiraterone was approved by the US Food and Drug Administration (FDA) and, in Australia, as post-docetaxel treatment in patients with CRPC.

Another agent in the armamentarium against mCRPC is enzalutamide (MDV-3100), an androgen receptor signalling inhibitor (ARSI) that binds the androgen receptor ligand site and thereby inhibits nuclear translocation of the androgen receptor. The results of the AFFIRM study,<sup>17</sup> comparing enzalutamide with placebo in patients previously treated with docetaxel, were recently published and showed a significant advantage in overall survival.

### Bone-targeted therapy

Radium-223 (Ra 223) is a first-in-class radiopharmaceutical that is an alpha particle emitter and calcium-mimetic. Ra 223 is taken up into the bone (especially osteoblastic metastases), where it delivers high energy, inducing DNA double-strand breaks. Ra 223 delivers high energy but short-range radiation, limiting damage to normal tissues. This drug is now available in Australia.<sup>18</sup>

### Discussion

The introduction of a variety of newer treatment options has changed the paradigm of metastatic CRPC. The results of recent trials have re-established hormonal treatment as a valid and survival-prolonging option in the pre- and post-chemotherapy settings.<sup>19,20</sup> However, a number of issues about how to integrate these agents into clinical practice persist. Another critical point is that the incidence of prostate cancer is disproportionately high in elderly men; therefore consideration should be given to life expectancy issues, functional status and the ability of a patient to tolerate potential side effects of these new therapies.

We believe that GPs have a very crucial role in helping patients make appropriate decisions. Initial responses to hormone-based therapies for prostate cancer are favourable, but patients ultimately will progress to CRPC, which displays resistance to traditional hormonal

manipulation. At this critical juncture, prior to referring the patients to either an oncologist or urologist, GPs can help to give patients a better understanding of the various treatment options and the side effects. This will help patients make more informed decisions about their treatment.

Until recently, therapies for CRPC were of a palliative nature and no proven survival benefit was established. In 2004, docetaxel was proven to prolong survival. Since then, use of a docetaxel-based regimen as first-line chemotherapy is considered a standard of care for men with CRPC.

It is now clear that other treatment modalities, including abiraterone acetate, administered before docetaxel chemotherapy, showed a statistically significant improvement in progression-free survival, compared with placebo, and a trend towards improvement in overall survival.<sup>12</sup> However patients in the post-docetaxel phase present the greatest challenge for ongoing research. To date, only a handful of agents such as cabazitaxel and the hypercastration agents (abiraterone and enzalutamide) have shown any benefit in this setting. None of the novel agents available have been compared with each other. Abiraterone is considered the most effective and least toxic agent and should be the agent of choice in CRPC.

In view of the persistence of androgen signalling in CRPC, results from additional ongoing phase 3 studies, particularly with novel therapies targeted at the androgen receptor, are also awaited with interest.

### Conclusion

In men with CRPC who have minimal metastatic burden and symptoms, no therapy with unequivocal effectiveness has yet been reported. Docetaxel is still considered the reference chemotherapy for patients with CRPC, with ongoing investigational efforts in docetaxel-naive, docetaxel combination and post-docetaxel domains.

No trial results to date support the addition of drugs other than low-dose

prednisone to docetaxel chemotherapy for the purpose of improving effectiveness. Cabazitaxel, abiraterone acetate and enzalutamide have all been shown to improve overall survival in men who progress after docetaxel. However, none of these agents have been compared with each other.

Abiraterone and enzalutamide are oral agents that have shown the most favourable toxicity profiles. To date, abiraterone has had the most favourable data with regard to palliative effects in this population, and on this basis would be considered the agent of first choice for most patients. However, more data about the palliative effects of enzalutamide are keenly awaited and will probably show results similar to abiraterone. Not all patients respond to abiraterone or enzalutamide, and almost all show disease progression despite treatment with these agents. For these men who have an adequate performance status and bone marrow function, second-line agents such as cabazitaxel should be considered. Further research is necessary to provide clinicians with the optimal choice, sequence or even combination of these drugs.

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