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Review article

Updates in Prostate Cancer: A Review on Management of Metastatic Disease

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Abstract

Prostate cancer is the most common non-cutaneous malignancy to effect men in Australia, and is the 5th leading cause of death. The management can be difficult in patients with a denovo presentation with metastatic castrate sensitive disease, or who progress to metastatic castration resistant prostate cancer. Since 2004 there have been multiple new agents for the treatment of this disease, both systemically and specifically for bony metastasis. This review aims to give doctors an overview of these medications, their side effects and their evidence base so they may provide good overall patient care.

Keywords: Prostate Carcinoma; Metastatic; Bony Disease; Castrate Resistant; Castrate Sensitive; Trial Review

Introduction

Prostate cancer is the most common non-cutaneous malignancy to affect men in Australia [1]. In 2011 it was the fifth leading cause of death in men, behind ischaemic heart disease, stroke, lung malignancy and Chronic Obstructive Pulmonary Disease [2]. Over the past decade treatment for prostate cancer has changed dramatically and there are new agents particularly for the treatment of metastatic castrate resistant prostate cancer. The following is a concise update on the treatments available and the evidence behind them.

In reviewing the treatment modalities for prostate cancer, both staging and the hormone sensitivity of the tumour need to be considered. Localised prostate cancer confers a relatively good prognosis, and the standard treatment modalities do not involve systemic chemotherapeutic agents. Treatment tends to involve surgical resection with radical prostatectomy, radiation therapy and androgen deprivation therapy (ADT). In some cases active surveillance with no intervention can also be an option.

The difficulty in management is seen in the setting of denovo presentation with metastatic castrate sensitive prostate cancer (mCSPC), or towards the end of the spectrum of disease, where the above therapies have eventually failed, leading to metastatic castration-resistant prostate cancer (mCRPC). It is well understood that ADT is not curative, and resistance eventually arises. The treatment for this can be considered in two separate sections; namely the systemic treatment of the disease itself for both castrate sensitive and castrate resistant disease; and the treatment of bony metastatic disease.

Systemic Treatment

Since 2004 the mainstay of treatment from a chemotherapeutic point of view has been docetaxel with prednisolone. The large phase III, randomised controlled trial TAX 327, showed

superiority as the first agent to show a survival benefit [3]. TAX 327 compared the then standard therapy of mitoxantrone and prednisolone, to docetaxel and prednisolone in patients with mCRPC. Prior to this trial, mitoxantrone and prednisolone had been used in a purely palliative sense, as the combination had been shown to reduce disease related pain, but had no survival benefit [3,4].

Docetaxel's survival benefit was then compounded by the CHAARTED trial, which was a study comparing ADT alone, to docetaxel with ADT combined in patients with mCSPC [5]. The docetaxel and ADT arm showed a survival benefit, particularly in those patients with high volume disease[5]. Finally, in May of 2015 the largest trial to date; STAMPEDE, a study examining men who had mCSPC, further confirmed the survival benefit of docetaxel [6]. This study is ongoing, with multiple arms.

One of these arms looked at the addition of docetaxel to standard ADT as initial treatment of denovo advanced prostate cancer. Thus far it has shown, on average a 10month survival benefit as compared to ADT alone[6],. Both CHAARTED and STAMPEDE have shown the early addition of docetaxel and prednisolone to standard ADT can improve overall survival in men with advanced hormone sensitive prostate cancer; as well as the already established survival benefit for mCRPC in TAX 327. Docetaxel is part of the taxane family, and causes cell apoptosis via microtubule depolymerisation and mitotic arrest [7]. Interestingly, docetaxel has also been shown to significantly reduce the nuclear androgen receptor of tumour cells; thus effecting tumour growth [8]. The side effects of this drug include myleosuppression and neurotoxicity specifically peripheral neuropathy.

Docetaxel is now being trialed in high risk, localized prostate cancer. RTOG-0521 is a trial comparing standard ADT and radiation therapy to standard ADT and radiation therapy with the early addition of docetaxel and prednisolone in men with high risk prostate cancer, defined as a Gleason score of 8-10, 9, PSA ≥20 ng/mL, or ≥ T2 stage disease [9]. In May 2015 the initial results were released and suggest, for the first time, that the early addition of docetaxel with prednisolone in this group procures a survival benefit [9]. Thus far it has shown a 30% reduction in the risk of death; with 10% increase in disease free survival [9]. This trial is ongoing, with a longer follow up period being needed to determine true outcomes.

It has been well established that some men with mCRPC will not respond to docetaxel, and inevitably, all patients will develop resistance to docetaxel based therapy [3]. The mechanism for drug resistance is multifactorial. These mechanisms include, tumour cells producing P-glycoprotein, which is the dominant drug efflux pump for both docetaxel and paclitaxel [10]. Another is β-Tubulin mutations that affect docetaxel binding, and render the drug less effective [10]. Treatment of docetaxel resistant prostate cancer was lacking until the advent of cabazitaxel, with the TROPIC trial [7,11,12]. Cabazitaxel is a second generation taxane that binds tubulin, and notably in this setting, has a poor affinity for p-glycoprotein [11]. The trials done with this drug showed a survival benefit in men with mCRPC who had developed docetaxel resistance, leading to the appropriation of this as the second line chemotherapeutic agent of choice. The side effect profile includes diarrhoea, nausea/vomiting, myalgia, myleosuppression and neurotoxicity.

Another avenue that was examined in the search for treatment for mCRPC was to target the androgen receptor pathway. Data suggests that the signaling of the androgen receptor is a crucial driver of growth in mCRPC [13]. The mechanism of castration resistance is multifactorial and includes increased synthesis of androgens, increased sensitivity to androgens (due to an overexpression of the receptor) and mutations in the androgen receptor leading to unrestrained activity [13-15].

The identification of the mechanism of resistance lead to the development of Abiraterone Acetate. It is a precursor to the active component, abiraterone, which resembles Pregnenolone structurally [16]. This inhibits 17α-hydroxylase/CYP17 which is an enzyme necessary for androgen synthesis [16]. This is expressed in not only prostate tissue, but also testicular and adrenal tissue. Inhibition of this enzyme leads to a reduction in androgen synthesis and testosterone levels leading to suppression of tumour growth [16].

Abiraterone Acetate was found to have a survival benefit against placebo after the COU-AA-301 trial, a large randomised, double blinded study [17]. This trial compared Abiraterone Acetate with prednisolone to Placebo with prednisolone in men with mCRPC who had progressed post treatment with docetaxel. Following this it proceeded to COU-AA-302 study which differed from the first trial, in that it looked at men who were chemotherapy naïve [18]. Both these trials confirmed a reduction in radiographic progression, and an increased overall survival in both men who had had docetaxel and those who had not with mCRPC [17,18]. It became approved for use in mCRPC 2011 in men who progressed post docetaxel; and has also been approved for use patients in whom chemotherapy is not suitable as a treatment post failure of standard ADT.

In regards to side effects, Abiraterone can lead to a reactive increase in corticotrophin-releasing hormone secondary to a pituitary response to the partial adrenal inhibition [16]. This leads to an increase in mineralocorticoid production, and symptoms similar to Conn's syndrome, with hypokalaemia, and hypertension. To circumvent this, Abiraterone is prescribed in conjunction with glucocorticoids [16]. Given the tendency to retain fluid; it is not given to patients with a reduced ejection fraction on cardiac echocardiogram. It can also cause bone pain, fatigue and anaemia [17].

Finally, the last drug to discuss in regards to systemic therapy is enzalutamide. Enzalutamide is a pure androgen receptor antagonist that has a higher affinity for the androgen receptor than previous drugs [3,19]. It also has the added ability to inhibit androgen receptor nuclear translocation and DNA binding [3,19]. It has been shown to produce a reduction in the PSA level in mCRPC; and in the AFFIRM trial, a stage III randomized controlled trial, showed a survival benefit against placebo, with a reduction in death of 37% [20].

Enzalutamide was also studied in chemotherapy naïve patients, in the PREVAIL trial. This also showed a survival benefit, and a 22% risk reduction of death [21]. Given this, as with Abiraterone Acetate, enzalutamide can be given in both mCRPC and in patients in whom chemotherapy is not suitable as a treatment post failure of standard ADT. Side effects include fatigue, hot flushes, hypertension and diarrhoea; however it is generally a well-tolerated drug.

It is worth noting that whilst cabazitaxel, abiraterone and enzalutamide have all shown a survival benefit in patients with docetaxel-resistant disease, and chemotherapy naïve disease against placebo, there have been no head-to-head trials comparing them.

Treatment of bony metastatic disease

In regards to the treatment of bony metastasis, all the above systemic therapies can control bony disease. However, there are treatments for the specific treatment of this. The first of these to discuss is bisphosphonate therapy, which has been readily available and in use since 2002, when trials first occurred with Zoledronic acid [22]. The trials compared Zoledronic acid to placebo and showed that Zoledronic acid reduced skeletal related events in prostate cancer with bony metastasis, and showed a modest but significant improvement in patient pain scores [22]. However it did not impact or improve disease progression and overall survival. Its mechanism of action is inhibition of osteoclastic bone resorption. The main limitation with Zolendronic acid is that it can cause renal impairment and the inability to use this drug in patients with a reduced creatinine clearance (<30ml/minute).

Its side effects include, fatigue, anaemia, myalgia and fever as some of the more prevalent ones reported [22]. It can also cause more serious side effects such as hypocalcaemia and osteonecrosis of the jaw. However, despite this, it was the only systemic treatment that reduced skeletal related events, until nearly a decade later, when Denosumab was first introduced. Denosumab has now been in use for several years. It is a fully human monoclonal antibody against RANK Ligand, a key regulatory factor in bone remodeling.

Denosumab, inhibits osteoclastic function, and mimics osteoprotegerin. It was shown in trials to be superior to Zoledronic acid in its ability to prevent skeletal related events and improve pain, in the setting of Breast and Prostate malignancy, and non-inferior in the setting of other tumours [23,24]. However, just like bisphosphonates, Denosumab has no effect on disease progression or overall survival [25].

Its side effect profile is similar to that of the bisphosphonates, however it can cause a more significant hypocalcaemia, and this needs to be monitored throughout therapy [25]. In this regard, Vitamin D levels should be checked prior to the commencement of therapy and corrected as well [25]. Other side effects include osteonecrosis of the jaw, atypical femoral fractures and hypophosphataemia [5].

Radium-223 dichloride, or Xofigo, is the newest drug used in the treatment of bony metastasis in mCRPC. Radium-223 dichloride is a targeted alpha emitter that selectively binds to areas of increased bone turnover within bone metastases, and emits high-energy alpha particles of short range [26]. This drug targets the sclerotic bone metastasis of prostate cancer, via is calcium mimetic properties, and binds into newly formed bone stroma of said metastasis [3,26].

The radiation emitted from the alpha particles causes double stranded DNA breaks that cause a highly potent and localized cytotoxic effect on the tumour; and as the alpha particles only have a short range, the toxic effects on bone marrow and adjacent healthy tissue are relatively reduced [26].

It has been found to reduce both serum PSA and ALP, and also procure a survival benefit [26,27]. It is the first treatment for bony metastasis that prolongs overall survival, and in the ALSYMPCA trial showed a 30% reduction in risk of death [26]. This drug has been reported to be very well tolerated, with only mild myleosuppression and gastrointestinal side effects [26].

The myleosuppresive effects may be increased in those patients with previous Docetaxel exposure, leading, in particular, to a larger incidence of thrombocytopaenia [28]. The risk of radiation exposure to other people is small. Prevention of radiation exposure to other people is mainly with good hygiene, this being avoiding contact with the patient's bodily fluids. At this time Radium-223 dichloride is not readily available in Australia.

Medication	Mechanism of Action	Indication	Side Effects
Docetaxel	Microtubule depolymerisation and mitotic arrest, leading to cell apoptosis	mCRPC – post failure of ADT Studies being done in high risk localised disease	Myleosuppression Neurotoxicity – peripheral neuropathy Hepatic dysfunction
Cabazitaxel	Tubulin binding leading to stabilisation of microtubules which interferes with mitotic interphase activity	mCRPC – post failure of Docetaxel	Myleosuppression Neurotoxicity – peripheral neuropathy Diarrhoea Nausea/vomiting Myalgia
Abiraterone Acetate	Inhibits 17α-hydroxylase/ CYP17, reducing androgen synthesis	mCRPC – post failure of Docetaxel Hormone sensitive prostate CA – if not suitable for Docetaxel	Hypokalaemia Hypertension Fluid retention Lethargy LFT derangement Bone Pain Anaemia
Enzalutamide	Androgen receptor antagonist Inhibits androgen receptor nuclear translocation and DNA binding	mCRPC – post failure of Docetaxel Hormone sensitive prostate CA – if not suitable for Docetaxel	Hot flushes Hypertension Lethargy Diarrhoea
Zoledronic Acid	Inhibits osteoclastic bone resorption	Bony metastasis of Prostate cancer – if suitable creatinine clearance	Hypocalcaemia Bone pain Osteonecrosis of the jaw Anaemia Myalgia Fatigue
Denosumab	Monoclonal antibody against RANKL Inhibits osteoclastic bone resorption	Bony metastasis of Prostate cancer – if suitable creatinine clearance	Hypocalcaemia Bone pain Osteonecrosis of the jaw Hypophosphataemia Atypical femoral fractures Anaemia Fatigue
Radium -223	Calcium mimetic, preferentially absorbed by bone Emits α particles	Bony metastasis of Prostate cancer – not readily available yet	Myleosuppression – mild GIT upset Thrombocytopaenia

Table 1. List of Medications used in Metastatic Castration Resistant Prostate Cancer, their mechanism of action, indication and side effects.

Conclusion

The treatments for metastatic castration resistant prostate cancer have developed to include a wide range of therapies, to improve both symptomatology and overall survival. Table 1 summarises these drugs for ease of reference. We hope this review allows doctors in the community to be better aware of the medications available, the evidence behind them and their side effect profiles to allow for better care of their patients.

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