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Review

Management of metastatic castration-resistant prostate cancer after first-line docetaxel

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ABSTRACT

Although chemotherapy, based on docetaxel, is now established in the management of metastatic castration-resistant prostate cancer (mCRPC), until recently, there has been no treatment licensed for use in the second line in men whose disease progresses during or after docetaxel therapy. This article reviews the classes of agents that have shown potential in this setting, notably chemotherapy drugs, hormonal therapies, immunotherapies, anti-angiogenic drugs, and clusterin-targeted therapy.

1. Introduction

Prostate cancer is the second leading cause of cancer death in men in the western world.[1] In Europe, more than 89,000 men are estimated to have died from prostate cancer in 2008,[2] and this figure is projected to rise.[3] As with most common solid tumours, outcomes for patients with prostate cancer are best when the disease is diagnosed in the organ-confined state.[4] However, a significant proportion of men (10–20%) have metastatic disease at presentation,[5] and others go on to develop distant metastases, despite receiving treatment at an earlier stage of their prostate cancer.[5]

Although hormonal treatments are the mainstay of prostate cancer management initially, the disease eventually becomes resistant to such interventions – i.e. the development of castration-resistant prostate cancer (CRPC).[4] In patients with metastatic disease, the onset of CRPC is almost inevitably associated with a poor prognosis and a high risk of developing significant symptoms that may be difficult to control.[6] Patients with localised CRPC are at high risk of progressing to the metastatic state.[7]

A landmark in the management of metastatic CRPC (mCRPC) was the publication in 2004 of the TAX 327[5] and Southwest Oncology Group 99-16[8] studies, which showed a significant survival benefit for patients treated with chemotherapy based on docetaxel, compared with mitoxantrone. The latter agent, whilst unlicensed for the treatment of prostate cancer in most of Europe, and lacking evidence of any survival benefit,[9,10] had become widely used to treat men with mCRPC. An updated survival analysis of the TAX 327 study showed that the median survival time was 19.2 months in patients given 3-weekly docetaxel, 17.8 months with weekly

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docetaxel and 16.3 months in the mitoxantrone arm.[11] Similar trends in survival were seen across all age groups. The Southwest Oncology Group trial randomised patients to either mitoxantrone or estramustine plus docetaxel.[8] The median overall survival (OS) was significantly longer in the group given docetaxel at 17.5 months versus 15.6 months, with the median time to progression extended from 3.2 months to 6.3 months. Significant cross over may account for small differences in OS.

Following these trials, 3-weekly docetaxel 75 mg/m^2 plus prednisone for up to ten cycles became the standard of care in most of Europe.

Since then, research interest has turned to the possibility of developing systemic non-ionising treatment for mCRPC that can be offered after docetaxel-based chemotherapy, with the aim of providing a further survival benefit. Patients being considered for further treatment following docetaxel fall into different groups – those who progress whilst being treated with docetaxel, those who are unable to tolerate it, and those who have responded well after eight to ten cycles and have, therefore, had a treatment break. This review focuses on treatments that have been undergoing clinical trials in this diverse population, and which may emerge into clinical practise over the next 5 years.

2. Second-line cytotoxic therapy

The median progression-free survival (PFS) for patients with mCRPC after docetaxel-based chemotherapy is 7.5 months,[12] and many of these patients remain in otherwise good health with good performance status.[13] In Europe, there are currently no cytotoxic regimens approved for use after docetaxel-based chemotherapy and, until recently, clinical trial results in this setting proved disappointing. However, more recent data suggest that selected patients may obtain clinical benefit from second-line cytotoxic chemotherapy, and one agent (cabazitaxel) has recently been approved in the USA for use in men with mCRPC who have already received docetaxel.

2.1. *Cabazitaxel*

Cabazitaxel is a semi-synthetic novel taxane. Like others of its class, it exerts its cytotoxicity by binding to tubulin and promoting polymerisation to form stable microtubules. This leads to inhibition of mitosis and promotion of cell death and apoptosis.[14,15] However, cabazitaxel differs from other taxanes, as it has been developed with the specific aim of circumventing taxane resistance. Unlike docetaxel, cabazitaxel is a poor substrate for the multi-drug resistance P-glycoprotein efflux pump,[26] and, therefore, has the potential to offer clinical benefit in patients for whom docetaxel has failed.

Phase I investigation of cabazitaxel in 25 patients with advanced solid malignancies (including prostate) showed anti-tumour activity, including in the docetaxel-resistant setting.[17] A multi-centre, single-arm, phase II study ($n = 71$) demonstrated that cabazitaxel was active and well tolerated in patients with taxane-resistant metastatic breast cancer.[16]

In 2010, phase III data from the TROPIC trial of cabazitaxel-based chemotherapy in men with mCRPC who had already received a docetaxel-based regimen were reported.[18] In this study, 755 patients were randomised to receive either cabazitaxel 25 mg/m^2 every 3 weeks plus prednisone or mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone.[18] Patients in each arm received up to 10 cycles of treatment. OS (the primary end-point) was significantly longer in the cabazitaxel arm (15.1 months) than in the control arm (12.7 months) (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.59–0.83). Subgroup analysis showed a benefit even for heavily pre-treated patients.

The most frequent grade 3 or 4 toxicity was neutropenia, which was reported in 81.7% of patients on cabazitaxel versus 58% on mitoxantrone, a difference reflected in the rates of febrile neutropenia (cabazitaxel, 7.5%; mitoxantrone, 1.3%). This incidence of grade $\geqslant 3$ neutropenia in the mitoxantrone group was considerably higher than the 22% incidence recorded in the mitoxantrone arm of TAX 327.[5] However, patients in this study were treated in the second line after docetaxel and this increase in toxicity reinforces the same excess in toxicity seen in other second-line studies. There was a treatment-related death rate of 2% in the mitoxantrone arm and 5% in the cabazitaxel arm, most commonly due to infection.[18] Notably, there were only two toxicity-related deaths – one in each study arm – among the 235 TROPIC patients treated in North American centres, suggesting there may be regional variations in the impact of drug toxicity.

There remain some criticisms of the TROPIC trial. Not all members of the study population were shown to be truly docetaxel resistant, and it is arguable that some of the patients might have benefited from docetaxel re-challenge. Whilst cabazitaxel showed significant benefits over mitoxantrone in terms of tumour and prostate-specific antigen (PSA) response, the difference in the level of pain control between the two regimens was not significant and quality-of-life data were not collected.

In addition, the dose of cabazitaxel used in TROPIC has been debated. Phase I trials recommended a dose of 20 mg/m^2 for future phase II and phase III studies.[17] However, the phase II breast cancer study cited above[16] initiated treatment at 20 mg/m^2 and, only in the absence of severe toxicity, increased the dose from cycle 2 onwards to 25 mg/m^2, the dose used from the outset in TROPIC. In fact, only a minority of patients in this breast cancer study were able to tolerate a dose increase and at least one dose reduction was required in 10% of patients.

Despite these criticisms, in light of these data, the US Food and Drug Administration (FDA) approved cabazitaxel for second-line treatment for patients with mCRPC previously treated with docetaxel. The FDA recommended consideration of primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) for patients with high-risk clinical features, including age $\geqslant 65$ years, poor performance status or the presence of serious co-morbidities. This is the first drug to be licensed in the USA for patients with mCRPC who have previously received docetaxel, and it is likely to be adopted as the standard of care in this setting. The European Medicines Agency has now also approved cabazitaxel for patients in the same clinical situation.

2.2. Satraplatin

Satraplatin, a third-generation oral platinum analogue, demonstrated encouraging activity in early trials,[19,20] but the results of the subsequent international phase III trial were disappointing.[21] A total of 950 patients with mCRPC were randomised to receive either satraplatin or placebo (2:1 ratio) plus prednisone after failure of one prior course of chemotherapy (51% prior docetaxel). There was a statistically significant but clinically modest increase in median PFS in the active treatment arm (satraplatin 11 weeks; placebo 9.7 weeks), but OS did not differ.[21] These results did not indicate a clinically relevant survival advantage for patients with mCRPC who received satraplatin following first-line chemotherapy. Satraplatin is not currently licensed in Europe for the treatment of prostate cancer.

2.3. Mitoxantrone

Mitoxantrone is licensed in the USA, but not in the UK or several other European countries, for first-line chemotherapy in patients with mCRPC. It was the chemotherapeutic standard of care prior to the approval of docetaxel in 2004. Mitoxantrone has modest activity in mCRPC in the first-line setting, but there is no evidence of a survival benefit.[9,10] In a phase II study of 41 patients treated with mitoxantrone after progression of mCRPC during or within 60 days of cessation of docetaxel therapy, eight had a confirmed PSA decline of $\geqslant$50% (20%; 95% CI, 9–35), with a median time to PSA progression of 2.3 months.[13] A population-based retrospective study of the effectiveness of sequencing docetaxel and mitoxantrone in the first- and second-line settings included 35 men who received mitoxantrone after failure of docetaxel.[22] Median OS in this group was 12 months (95% CI, 7.8–16.2), and there was a 12% PSA response rate. Of concern, however, 46% of the patients required dose modifications because of toxicity.[22]

A retrospective analysis of data from the pivotal TAX 327 study of first-line docetaxel versus mitoxantrone found that among 232 patients who crossed over (docetaxel to mitoxantrone or vice versa) the median survival after crossover was 10 months and did not depend on the direction of crossover.[23] PSA response ($\geqslant$50% reduction) occurred in 15% of 71 men who received mitoxantrone after docetaxel and in 28% of 25 men who received docetaxel after mitoxantrone. Median PSA PFS was 3.4 months for mitoxantrone after docetaxel and 5.9 months for docetaxel after mitoxantrone.[23] These limited data suggest that the modest benefits and good tolerability associated with first-line mitoxantrone may not be replicated in second-line treatment.

2.4. Repeated docetaxel

Various small-scale studies have investigated whether patients whose response to first-line docetaxel chemotherapy was sustained after completion remained sensitive to the same drug. A retrospective analysis including 10 patients who received first-line docetaxel (3-weekly) followed by second-line docetaxel (3-weekly) found that seven of the patients responded to docetaxel re-treatment, with a PSA reduction of >50%, and the remaining three patients had a symptomatic improvement.[24] Three patients who responded to both first-line and second-line docetaxel were re-challenged again with docetaxel, and all achieved a PSA reduction of $\geqslant$50%. The median treatment-free intervals before second- and third-line treatment were 24 and 26 weeks, respectively. Although there was grade 3 or 4 neutropenia in 2.5% of first-line cycles, 7% of second-line cycles and 12% of third-line cycles, patients otherwise tolerated re-treatment well.[24] This small study suggests that patients who initially respond to docetaxel may maintain their sensitivity to subsequent re-treatment without a significant rise in unacceptable toxicity. It does not, however, confirm that docetaxel re-challenge offers clinical benefit for selected patients.

In the ASCENT study, docetaxel 36 mg/m^2 was given on days 1, 8 and 15 of a 28-day cycle in combination with either calcitriol 45 μg or placebo.[25] Patients could suspend treatment if their PSA level was reduced by $\geqslant$50% and reached $\leqslant$4 ng/ml. Docetaxel re-challenge was allowed on PSA progression for patients who had shown a previous good response to the treatment. Of 33 patients who were re-challenged, 15 (45.5%) showed a PSA decline of $\geqslant$50% on treatment resumption.[25] The range of patients who received intermittent chemotherapy on the ASCENT trial was broad, but generally, patients who received intermittent chemotherapy appeared to have had more favourable prognostic features before chemotherapy than those who did not. Although these data add some support to the notion of docetaxel re-challenge, it must be noted that this study was based on a small sample of patients receiving a non-standard regimen.

Another retrospective study identified 31 patients who were reportedly refractory to 3-weekly docetaxel after a median of 16 weeks' treatment and were switched to weekly docetaxel 30 mg/m^2.[26] Twenty-five (80%) showed a median PSA decline of 46%, and patients stayed on weekly treatment for a median of 16 weeks. These data suggest that, for some patients, docetaxel sensitivity may be schedule-dependent. However, the study lacked a clear definition of resistance to 3-weekly docetaxel, and it is possible that patients were switched before resistance had developed. Furthermore, it is important to remember that patients treated with weekly docetaxel in the TAX 327 study had inferior outcomes, compared with those who received the 3-weekly regimen.[11]

These small-scale studies do suggest that some patients may retain sensitivity to docetaxel after completion of first-line therapy, and the existing data indicate that repeat treatment is reasonably well tolerated. However, the clinical benefits of re-treatment with docetaxel will need to be clarified before such a strategy can be recommended.

One particular concern with docetaxel re-treatment is documented evidence of the drug's high substrate affinity for multi-drug resistance proteins, notably the multi-drug resistance P-glycoprotein efflux pump – a property shared by many taxanes.[17] Use of second-line docetaxel in the setting of taxane resistance could risk exposing the patient to treatment side-effects without concomitant treatment benefits.

2.5. Non-taxane microtubule-targeting agents

The epothilones are non-taxane, microtubule-stabilizing agents. Two members of this new drug class – ixabepilone

and patupilone – are currently being studied in mCRPC. Despite being structurally similar, the two agents have distinct toxicity profiles. The primary dose-limiting toxicity of ixabepilone is neuropathy, whereas for patupilone, it is diarrhoea.[27] In a phase II trial, 42 chemotherapy-naïve patients with mCRPC were given ixabepilone 40 mg/m^2 every 3 weeks. There were 14 confirmed PSA responses (33%; 95% CI, 20–50%); 10 (24%) patients had a PSA reduction >80%, and two patients achieved an undetectable PSA.[28] The median PFS was 6 months, with an OS of 18 months. The most common grade 3 toxicities were sensory neuropathy and myelosuppression.

A randomised phase II trial in 82 patients with mCRPC who had progressed during or within 60 days of docetaxel chemotherapy, compared ixabepilone 35 mg/m^2 every 3 weeks with mitoxantrone 14 mg/m^2 every 3 weeks, each in combination with prednisone and continued until progression.[13] The PSA results were similar in both groups, with a $\geqslant$50% decline in 17% of the ixabepilone group and 20% of the mitoxantrone group. A prior taxane response was associated with a significantly increased likelihood of response to either second-line therapy. OS was similar in both groups, at 10.4 months for ixabepilone versus 9.8 months for mitoxantrone.

After a planned crossover, 11% and 27% of patients demonstrated third-line PSA responses to ixabepilone and mitoxantrone, respectively, suggesting clinical non-cross resistance between the two regimens. Because of this finding, a phase I/II, multicentre, dose-escalation study investigated ixabepilone in combination with mitoxantrone administered every 3 weeks along with prednisone in 36 patients who had received prior taxane-based chemotherapy.[29] Of 21 patients who received mitoxantrone 12 mg/m^2 together with higher doses of ixabepilone ($\geqslant$30 mg/m^2), nine (43%) had a $\geqslant$50% PSA decline. Because of high rates of grade 3 or 4 neutropenia, the authors recommended mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2 every 21 days with pegfilgrastim 6 mg on day 2, and continuous prednisone 5 mg twice daily for the ongoing phase II study.

In a phase II study of mCRPC patients who had progressed within 6 months of docetaxel, patupilone 8 mg/m^2 every 3 weeks was well tolerated, with PSA declines of >50% in 45% patients. Grade 3/4 adverse events (AEs) included fatigue, diarrhoea and anorexia.[30]

Together, these data suggest that the epothilones have potential as a class of agents for patients with mCRPC, and ongoing trials are further investigating their role.

Eribulin (E7389) is a non-taxane microtubule dynamics inhibitor, which is being studied in a variety of solid tumours. The FDA has recently approved its use in metastatic breast cancer and there is interest in its role in mCRPC. A multi-centre phase II study of 108 patients with mCRPC included 50 who had previously been treated with taxanes.[31] Eribulin demonstrated activity, with a PSA decline of $\geqslant$50% in 8.7% of pre-treated patients and 22.8% of chemotherapy-naïve patients.

3. Hormonal therapies

Several pre-clinical and clinical studies have shown that castration-refractory prostate-cancer cells continue to express high levels of androgen receptor (AR) and that AR-dependent signalling pathways remain active even at castrate testosterone levels.[32] Rising PSA, an indication that AR signalling has been reactivated, is the result of selective and/or adaptive oncogenic changes in the AR, of which AR over-expression is the most common.[32] Furthermore, it is now clear that cancers previously termed 'hormone-refractory' may retain sensitivity to further hormonal manipulation.[4]

3.1. *MDV3100*

MDV3100 is a potent AR antagonist that has no agonist activity.[33] A phase I/II trial of MDV3100 has demonstrated substantial anti-tumour effect in men with mCRPC, with a $\geqslant$50% decline in the baseline PSA at 12 weeks in 57% of chemotherapy-naïve and 36% of post-chemotherapy patients.[33] The median time to progression was 47 weeks for radiological progression. The most common grade 3 or 4 AE was dose-dependent fatigue, which generally resolved after dose reduction. A phase III, randomised, placebo-controlled trial of MDV3100 in men with progressive advanced prostate cancer who have received previous docetaxel therapy (AFFIRM) completed enrolment in November 2010. Another phase III trial (PREVAIL) is now evaluating this agent in chemonaïve patients.

3.2. *Corticosteroids*

The primary rationale for administering corticosteroids in mCRPC is that some patients still have disease that is stimulated by weak androgens of adrenal origin, and that these androgens may be suppressed by corticosteroids through the generation of negative feedback on secretion of adrenal corticotrophic hormone.[34] Glucocorticoids have been shown to suppress interleukin-6,[35] and dexamethasone has been shown to inhibit angiogenesis in xenograft models,[36] findings that suggest these agents may also have a direct cytotoxic effect that is not yet fully identified.

In one study of patients with symptomatic bony metastases, the response to low-dose prednisolone treatment was assessed by measuring the requirement for analgesia.[37] A 38% improvement in pain was recorded at 1 month, and maintained for a median of 4 months in 19% of patients. Biochemically, there was a decrease in concentration of serum testosterone among patients in whom it was not initially suppressed, and a decrease in serum levels of androstenedione and dehydroepiandrosterone sulphate in over 50% of patients.[37] Other small studies using dexamethasone (0.5–2 mg/day) have shown a decline in PSA, associated with increased median survival and symptomatic response.[38–40] As a treatment strategy, corticosteroids provide low-cost therapy with manageable toxicity and possible clinical activity against prostate cancer.

3.3. *Oestrogens*

Oestrogens, particularly diethylstilbestrol (DES), were a primary medical treatment for metastatic prostate cancer until they were superseded by agonists of luteinising-hormone-releasing hormone. There is renewed interest in these drugs, particularly following the recent description of oestrogen

receptor (ER)-II, which is strongly expressed in normal prostate epithelium, and lost in prostate cancers.[41]

In phase II trials in mCRPC, biochemical response rates to DES, DES-diphosphate and the oestrogenic herbal therapy PC-Spes, vary from 23% to 86%.[42] In a small study of patients previously treated with docetaxel, 1 mg of DES induced a PSA response of ⩾30% in 25% and ⩾50% in 15% of patients, with a median PFS of 3.7 months and a median OS of 20.7 months.[43] Oestrogens are generally well tolerated, although there is an excess of thromboembolic events among recipients. Toxicity may be attenuated by use of lower doses and by parenteral routes of administration that avoid hepatic first-pass metabolism.

3.4. *Ketoconazole*

Ketoconazole inhibits multiple members of the cytochrome (CYP) P450 metabolic enzyme family. Although a relatively weak inhibitor of CYP17 (which is fundamental to adrenal steroid sex hormone synthesis), ketoconazole reduces synthesis of cortisol and suppresses androgen production. It has moderate anti-tumour activity in CRPC, with biochemical response rates in phase II/III studies ranging from 31% to 62%, and a median duration of response of up to 7.7 months.[44–47] However, its use requires replacement hydrocortisone to prevent adrenal insufficiency and, therefore, at least part of the observed activity may be attributed to concurrent corticosteroid administration. Furthermore, an observed increase in androgenic steroids at disease progression among patients receiving this agent may indicate incomplete target blockade.[47]

Ketoconazole has been explored in combination with docetaxel. A phase I study in 42 patients with mCRPC found that the addition of high-dose ketoconazole significantly increased patients' exposure to weekly docetaxel (in a dose-dependent manner).[48] Decreases in PSA of ⩾50% were seen in 62% of patients. Median OS was 22.8 months, and was significantly greater in docetaxel-naïve patients than in patients who had been pre-treated with docetaxel (36.8 versus 10.3 months, $p = 0.0001$).[48] The authors concluded that additional, larger trials of docetaxel combined with ketoconazole are warranted.

Attempts to compare ketoconazole as secondary hormonal therapy with docetaxel, such as the Eastern Cooperative Oncology Group (ECOG) 1899 have been unsuccessful with this trial closing early due to poor accrual. Retrospective reviews have explored the efficacy of ketoconazole in patients who have previously received docetaxel. In one of these, 26 of the 32 evaluable patients had responded to docetaxel chemotherapy previously.[49] On treatment with ketoconazole, which commenced immediately after progression on docetaxel in 20 cases, 8 patients (25%) had a PSA decline of ⩾50%. They did not find a significant association between previous PSA response to chemotherapy and the PSA response with ketoconazole.[49] In another analysis of 11 patients with mCRPC who received ketoconazole after progressing on docetaxel, four (36%) achieved a PSA decline of ⩾50%, including three who had not achieved a significant response to prior docetaxel and three who did not receive concomitant corticosteroids.[50]

3.5. *Abiraterone acetate*

Abiraterone acetate is a highly selective irreversible inhibitor of CYP17, and blocks non-gonadal androgen production. It is 10–30-fold more potent against this target than ketoconazole.[51]

A phase I trial in 21 chemotherapy-naïve men with mCRPC found that abiraterone acetate 1000 mg once daily was well tolerated and efficacious.[52] The anticipated toxicities – hypertension, hypokalaemia and lower-limb oedema – were successfully managed with mineralocorticoid receptor antagonists, such as the selective aldosterone inhibitor, eplerenone. Declines in PSA of ⩾30%, ⩾50% and ⩾90% were observed in 66%, 57% and 29% of patients, respectively. Radiological regression, normalisation of lactate dehydrogenase and improved symptoms with a reduction in analgesic use were also documented. The addition of dexamethasone 0.5 mg once daily resulted in successful salvage in four of 15 patients (26%) who had started to progress. The combination of corticosteroid with abiraterone also prevented secondary mineralocorticoid production.[52]

Early phase I/II data for abiraterone acetate were encouraging[51,53–55] and rapidly led to completion of a pivotal trial programme. The results of COU-AA-301, a double-blind, randomised, placebo-controlled trial of prednisone 10 mg/day with or without abiraterone 1000 mg/day were presented in 2010.[56] This trial included 1,195 patients with mCRPC who had received one or two prior lines of chemotherapy (one of which must have contained docetaxel). Of note, patients were encouraged to continue trial medication until biochemical, radiological and symptomatic progression had all been observed.[56]

The study was terminated early after a planned interim analysis demonstrated clear superiority of the investigational agent. The HR for survival was 0.65 (95% CI, 0.54–0.77; $p < 0.0001$), with median survival of 14.8 months, compared with 10.9 months in the control arm.[56] The most common AEs were fluid retention and hypokalaemia, with a small excess of biochemical liver function derangement, hypertension and cardiac disorders.[56] On the basis of these results, marketing authorisation is being sought in Europe and has recently been granted in the USA.

A further phase III study in patients who have not previously received chemotherapy (COU-AA-302) has completed accrual, although results are not yet available.

4. Immunotherapy

The underlying principle of immunotherapy is to stimulate the patient's immune system to create an anti-tumour effect. Multiple approaches to immunotherapy have been taken in many tumour types but, until recently, progress in prostate cancer was disappointing. Two large, randomised, phase III trials of GVAX, a cell-based, gene-transduced multi-antigen vaccine developed using two human prostate cancer cell lines, were both terminated following futility analysis in one (VITAL-1),[57] and excessive deaths in the trial arm in the other (VITAL-2).[58]

4.1. *Sipuleucel-T*

Sipuleucel-T uses extra-corporeal dendritic cell stimulation to induce the patient's own T-cell mediated immunity. In a phase III, placebo-controlled study of patients with asymptomatic mCRPC ($n = 127$, including 7 patients who had received prior chemotherapy), there was no significant difference between sipuleucel-T and placebo in time to progression.[59] However, 3-year follow up showed a median survival benefit of 4.5 months in the sipuleucel-T group.

The placebo-controlled IMPACT study of sipuleucel-T, conducted in 512 patients with asymptomatic or minimally symptomatic mCRPC, included 18% who had received prior chemotherapy, with the majority of these in both arms having received docetaxel.[60] Of note, exclusion criteria included visceral metastases, previous treatment with more than two chemotherapy regimens or chemotherapy within the previous 3 months. The most common AEs were chills, fever, headaches and influenza-like illness. There was a median survival advantage of 4.1 months for sipuleucel-T versus placebo, and the 3-year survival rate also improved significantly (sipuleucel-T, 31.7%; placebo, 23%; $p = 0.032$).[60,61] The Kaplan-Meier estimate of the median time to subsequent docetaxel was 12.3 months in the treatment arm and 13.9 months in the placebo group.

A thorough formal evaluation in post-chemotherapy patients has not been performed, although the treatment effect of sipuleucel appeared to have been slightly greater in those who had previously received chemotherapy. Based on these results, the FDA approved sipuleucel-T in May 2010 for the treatment of asymptomatic or minimally symptomatic mCRPC.

4.2. *Ipilimumab*

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has emerged as a potential anti-cancer target. Ipilimumab is a fully human antibody that binds to CTLA-4 and blocks its activity, resulting in a sustained immune response. A phase III trial has shown a significant survival advantage for patients with advanced melanoma.[62]

In prostate cancer, a phase II study of ipilimumab in combination with radiotherapy has shown that PSA declined by $\geqslant$50% in 10 out of 45 patients, and the median duration of response was 23 weeks.[63] Adverse immune-related events included diarrhoea, rash and hepatitis. Several trials are ongoing, including one randomised, double-blind, phase III study comparing ipilimumab with placebo following radiotherapy in patients with mCRPC who have received prior docetaxel, and another in chemonaïve patients.

5. Anti-angiogenic agents

There remains interest in angiogenesis as a target for prostate cancer treatment. Whilst many of these trials have been in chemotherapy-naïve mCRPC patients, the results may alter future trials in the later setting. In a trial of bevacizumab in combination with docetaxel to patients with treatment-naïve mCRPC,[12] the statistically significant benefits in PSA response and overall response rates did not translate into an OS difference because of excess toxicity in the experimental arm.

A phase II trial of bevacizumab combined with thalidomide, docetaxel and prednisone in patients with chemotherapy-naïve mCRPC found that 90% of patients had PSA declines of $\geqslant$50%.[64] The median time to progression was 18.3 months with a median OS of 28.2 months. Whilst the investigators report that toxicities were manageable, all patients developed grade 3 or 4 neutropenia, which would be of serious concern in second-line therapy.

Despite early signs of clinical activity of the oral vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors, sunitinib and sorafenib, in this setting,[65,66] a large randomised, placebo-controlled trial of prednisolone with or without sunitinib (37.5 mg continuous daily dosing) in post-docetaxel mCRPC was recently terminated early due to lack of activity.

XL184 (cabozantinib) is an oral potent inhibitor of Met and VEGFR-2. Initial results of a phase II, adaptive, randomised discontinuation trial suggest activity against CRPC.[67] Eligible patients have CRPC with measurable disease and disease progression on $\leqslant$1 prior non-hormonal systemic treatments. Forty-five percent of patients entered at the time of reporting had received prior docetaxel. At this point, there were 24 patients whose responses were evaluable, of whom five had a partial response in measurable disease and 6 had a PSA decline of $\geqslant$50%. Cases of complete or near complete resolution of bony lesions in both the prior chemotherapy and chemonaïve group have also been reported.[67]

6. Clusterin-targeted treatment

Clusterin is a cytoprotective chaperone protein that promotes cell survival, and has been identified as a potential target for cancer treatment. Its production is inhibited by the antisense oligonucleotide, custirsen.[68] A phase II study in 82 chemotherapy-naïve patients with mCRPC found that the addition of custirsen to first-line docetaxel increased median OS to 23.8 months, compared with 16.9 months for docetaxel alone.[69] In addition, at least 58% of patients in the custirsen arm had a PSA decline of $\geqslant$50%. Similar results were obtained in patients who relapsed within 6 months of first-line chemotherapy.[70] Based on these results, a randomised, placebo-controlled, double-blind, phase III study is now open, evaluating the benefit of adding custirsen to docetaxel re-treatment in men with mCRPC who have previously responded to docetaxel.

Table 1 summarises ongoing trials in second line therapy for mCRPC.

7. Individualised therapy

The ultimate aim of developments in this field would be to move toward individualised therapy. Prostate cancer is a highly heterogeneous disease and there is an urgent need for predictive biomarkers, to help guide the stratification of patients and therapies. A wide range of blood- and urine-based biomarkers are at various stages of development such as human kallikrein 2, early prostate cancer antigen, transforming growth factor-beta 1 and ETS Gene Fusions. Circulating tumour cells (CTC) have been the subject of intense

Table 1 – Ongoing trials of second line therapy for mCRPC.

Target	Agent	Phase	Design	Primary endpoint	Estimated number of patients	Clinical trials reference number
Androgen synthesis (CYP17)	Abiraterone plus prednisolone	III	Randomised, placebo controlled	OS	1,158	NCT00638690
Androgen synthesis	TAK700	I/II	Dose ranging	Safety	123	NCT00569153
Androgen analogue	HE3235	I/II	Dose ranging	Safety, PK, activity	64	NCT00716794
Androgen receptor	MDV3100	III	Randomised, placebo controlled	OS	1,200	NCT00974311
Clusterin	Custirsen plus docetaxel and prednisolone	III	Randomised, placebo controlled	Pain, palliation	292	NCT01083615
CTLA-4	Ipilimumab	III	Randomised, placebo controlled	OS	800	NCT00861614
IGF-1 receptor	Cixutumumab or ramucirumab plus mitoxantrone and prednisolone	II	Randomised, open label	PFS	132	NCT00683475
IGF-1 receptor	Figitumumab plus docetaxel and prednisolone	II	Randomised, open label	PSA and tumour response	120	NCT00313781
mTOR and VEGF	Temsirolimus and bevacuzimab	I/II	Dose ranging	MTD	34	NCT01083368
VEGF receptor	Cediranib	II	Interventional, open label	PFS	59	NCT00436956
VEGF receptor	Cediranib with/without dasatinib	II	Randomised, open label	PFS	50	NCT01260688
TK	Sunitinib	II	Interventional, open label	PFS	50	NCT00748358
Androgen receptor	AZD3514	I	Interventional, open label	Safety and tolerability	50	NCT01162395
DNA and mTOR	Carboplatin, everolimus, and prednisone	II	Interventional, open label	TTP	56	
DNA and tubulin formation	Azacitidine, docetaxel and prednisone	I/II	Interventional, open label	MTD and PSA response	42	NCT00503984
Tubule formation	Cabazitaxel	III	Single arm, open label	Early access to cabazitaxel	808	NCT01254279
MAO and tubulin formation	Phenelzine sulphate and docetaxel	II	Interventional, open label	PSA response	20	NCT01253642
EGFR	Mitoxantrone with or without cetuximab	II	Randomised, open label	TTP	130	NCT00661492
Clusterin	OGX-011 and docetaxel	I/II	Interventional, open label	Safety	60	NCT00327340
DNA synthesis	Pemetrexed	II	Interventional, open label	PSA response	43	NCT00216099
VEGF	Enzastaurin	II	Interventional, open label	Objective response rate and PFS	72	NCT00428714
Hsp90	STA-9090	II	Interventional, open label	PFS	51	NCT01270880
Endoglin	TRC105	I/II	Interventional, open label	MTD	90	NCT01090765
Microtubule growth	Eribulin	II	Interventional, open label	PSA response	110	NCT00278993
Microtubule growth	Retaspimycin	II	Interventional, open label	Treatment response	19	NCT00564928
PSA production	PSA/TRICOM vaccine and 153Sm-EDTMP radiation	II	Randomised, open label	PFS	68	NCT00450619

OS, overall survival; PK, pharmacokinetics; PFS, progression-free survival; IGF, insulin-like growth factor; PSA, prostate-specific antigen; VEGF, vascular endothelial growth factor; MTD, maximum tolerated dose; TK, tyrosine kinase; TTP, time to progression; MAO, monoamine oxidase.

interest. In one multi-centre prospective study, blood was taken from mCRPC patients with progressive disease starting a new line of chemotherapy both before treatment and monthly thereafter. CTC counts following treatment were the strongest independent predictor of OS and predicted OS better than other markers such as PSA reduction.[71] A technique for assessment of CTC has now been approved by the FDA in the US as a prognostic indicator for patients with metastatic tumours, including prostate.

Disease response to treatment can be difficult to assess. Previously, some progression dates may have been erroneously assigned due to flares in PSA, pain or on a bone scan. The PCWG2 guidelines were published in 2008[72] and set out guidelines for the assessment of mCRPC to treatment, but there are still areas of debate. Of note, they recommend that early changes in PSA and/or pain are not acted on without other evidence of progressive disease.

Interestingly, one group has explored the factors influencing survival after treatment with first-line chemotherapy, using data from the TAX 327 study.[73] Using multi-variable analysis, pain, performance status, alkaline phosphatase, number of sites of metastatic disease, liver metastases, haemoglobin, PSA and time since diagnosis were all important factors associated with poor prognosis. Treatment was continued until toxicity, progression or death. There was a highly significant difference in OS between the group who developed disease progression whilst on chemotherapy (median OS 11.4 months), compared with those who completed the planned course of chemotherapy and then progressed (median 20.9 months).[73]

In addition, the number of ways in which the disease was considered to have progressed (PSA rise, increasing pain or tumour size), the duration of first-line chemotherapy and whether progression occurred during chemotherapy independently predicted post-progression survival. They used these data to develop a post-first-line treatment nomogram of survival.[73]

8. Conclusion

Although prostate cancer is one of the most common causes of cancer death and morbidity in men, the pace of medical progress for those with advanced disease has, for some time, lagged behind that for patients with other common solid tumours. This pace is now quickening, however, and new treatments are, at last, almost within reach.

The pivotal studies of docetaxel marked a paradigm shift in the management of mCRPC. As a result, incremental OS has become the primary goal of new systemic interventions for these patients. Furthermore, it has become clear that there is a large group of men able to benefit from further systemic treatment after the failure of docetaxel. Cabazitaxel is the first therapy licensed specifically for this population.

The opportunity to offer second line and subsequent lines of therapy for mCRPC relies in part on timely delivery of first-line chemotherapy in men with minimal symptoms – a strategy that helps to prevent or delay some of the highly morbid consequences of disease progression, such as spinal cord compression. The importance of timely first-line treatment is particularly marked when the second-line treatment demands significant reserves of organ function and performance status, as is the case with chemotherapy and immunotherapy.

In the future, the choice of effective therapies available after docetaxel is likely to include treatments from widely differing therapeutic classes, and the sequence in which these agents are used will become an important consideration in the management of mCRPC. Currently, there is no evidence to guide such decisions. Where a new treatment is associated with significant side-effects, the physician and patient may feel that it is advisable to delay its use until no alternative option remains. On the other hand, by delaying a therapy, the opportunity for efficacy may be missed. Looking forward, there is clear need for trials that explore the timing, sequencing and combined use of the emerging therapies for mCRPC post-docetaxel.

Conflict of interest statement

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