Review

Evolving role of chemotherapy in castration-resistant prostate cancer

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Practice Points

- Mitoxantrone has beneficial effects on quality of life and pain reduction in patients with metastatic castration-resistant prostate cancer.
- The TAX 327 and SWOG 9916 trials demonstrate an overall survival benefit in metastatic castration-resistant prostate cancer.
- Multiple trials have explored combination regimens with platinum-based compounds and docetaxel.
- Cabazitaxel has been shown to have an overall survival benefit in second-line chemotherapy in metastatic castration-resistant prostate cancer after treatment with docetaxel.
- Mechanisms of taxane resistance are multifactorial and need further evaluation.
- The future of chemotherapy may be in taxane-based combinations, in particular with hormonal agents, but also with angiogenesis inhibitors, immunomodulators, immunotherapy or novel agents.

SUMMARY The role of chemotherapy in castration-resistant prostate cancer has evolved greatly over the past several decades. However, at this time, docetaxel remains the only first-line chemotherapy option that improves survival. More recently, the novel taxane cabazitaxel (plus prednisone) was found to prolong overall survival in metastatic castration-resistant patients who had progressed during or after docetaxel therapy. The addition of new hormonal agents, immunologic-based therapies, angiogenesis inhibitors and other small molecules to docetaxel is under investigation. To date, the results of such combination therapies have been disappointing but there is a significant optimism surrounding the ongoing studies.

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Prostate cancer is the second leading cause of cancer-related deaths in men in the USA, with an estimated 240,890 new cases and 33,279 deaths in 2011 [1]. In approximately 80% of patients, primary androgen ablation helps to relieve symptoms and decrease levels of PSA [2]. Although many men never develop metastatic disease, those who have disease progression despite testosterone levels less than 50 ng/ml are defined as castration-resistant. It is to be noted that, while the median age of patients at diagnosis is 69 years old, the median age of patients with metastatic disease is 79 years of age [101]; therefore, we are dealing with a geriatric population. For patients with symptomatic or rapidly progressing disease chemotherapy not only improves survival but also has a significant palliative effect. The role of chemotherapy has changed greatly over the last several decades, evolving from rarely used, to providing palliative benefit, to eventually improving survival [3].

Mitoxantrone

In the treatment of prostate cancer, corticosteroids were found to have some activity against the cancer with beneficial effect on quality of life (QOL) [4]. In addition, mitoxantrone had demonstrated activity in prostate cancer [5]. In 1992, the Cancer and Leukemia Group B (CALGB) compared hydrocortisone to hydrocortisone plus mitoxantrone in CALGB 9182 [6]. There was found to be no difference in overall survival (OS) between the two groups, but there was a benefit in pain control with hydrocortisone plus mitoxantrone compared with hydrocortisone alone.

In the mid 1990s, a randomized Phase III trial compared mitoxantrone plus prednisone with prednisone alone in men with metastatic castration-resistant prostate cancer (mCRPC) [7]. The chemotherapy combination was found to provide superior palliative benefit [8]. Mitoxantrone plus prednisone was approved by the US FDA in 1996 for the treatment of castration-resistant prostate cancer (CRPC). For symptomatic patients, mitoxantrone plus prednisone improved QOL and reduced pain [8,9]. However, mitoxantrone plus prednisone was not found to improve OS. A cost–utility analysis did find that palliative improvements (including reduction of pain) led to fewer hospital admissions and thereby offset the cost of treatment [10].

Docetaxel versus mitoxantrone for prostate cancer

Treatment for CRPC remained palliative and new options were needed not only to relieve pain and improve QOL but also to improve OS. Preclinically, docetaxel was shown to have activity in prostate cancer cell lines. In a Phase II trial, Beer *et al.* demonstrated that docetaxel was well tolerated in 25 patients treated with docetaxel 36 mg/m^2 weekly for 6 weeks. Eleven out of 24 patients with an elevated PSA had a PSA response (defined as a reduction in serum PSA levels of at least 50%) [11]. In 35 patients who received docetaxel at 75 mg/m^2 every 21 days, Picus and Shultz showed seven patients (20%) had a more than 80% decline in PSA and 16 (46%) had a decline of more than 50%. Six additional patients had a PSA decline of 40–50% [12]. In another Phase II study conducted by Friedland *et al.*, a 38% PSA response rate was seen in 16 patients, half of whom had received prior chemotherapy [13].

Two Phase III trials established docetaxel as standard first-line therapy in mCRPC based on an improved OS. TAX 327 was a randomized, nonblinded study comparing docetaxel (given either weekly or every 3 weeks) plus daily prednisone with mitoxantrone plus prednisone [14]. Eligible patients had confirmed metastatic adenocarcinoma of the prostate and had disease progression during hormonal therapy [14]. Patients received either 75 mg/m^2 of docetaxel on day 1 of a 21-day cycle or 30 mg/m^2 of docetaxel on days 1, 8, 15, 22 and 29 of a 6-week cycle. The third arm received 12 mg/m^2 of mitoxantrone on day 1 of a 21-day cycle. All patients received 5 mg of prednisone twice daily starting on day 1. The primary end point was OS with secondary end points of pain response, PSA declines and QOL.

One thousand and six patients underwent randomization from March 2000 to June 2002. The baseline characteristics of all three groups were well balanced. A survival benefit was found in the group who received docetaxel every 3 weeks when compared with the mitoxantrone group ($p = 0.009$), with a median survival of 18.9 months. The hazard ratio (HR) for death was 0.76 in the group who took docetaxel every 3 weeks (95% CI: 0.61–0.94). Survival was not found to be significantly higher in the group given weekly docetaxel when compared with mitoxantrone (17.4 vs 16.5 months; HR:

0.91; 95% CI: 0.75–1.11; p = 0.36). Predefined reductions in pain were seen more frequently in the every-3-week docetaxel group with a 35% reduction compared with 22% on mitoxantrone (p = 0.01). PSA declines of 50% were higher in the two docetaxel groups than in the mitoxantrone group and were both statistically significant with p < 0.001.

Adverse events (AEs) were more predominant in the docetaxel groups. Although febrile neutropenia was rare, grade 3 or 4 neutropenia was seen in 32% of patients in the every-3-week docetaxel group, 1.5% of patients treated with weekly docetaxel and 2% of patients treated with mitoxantrone. A total of 10% of patients treated with mitoxantrone exhibited cardiac dysfunction (including impaired left ventricular ejection fraction).

Overall, this Phase III study revealed a survival benefit in patients treated with docetaxel every 3 weeks. An updated survival analysis revealed that 18.6% of patients treated with docetaxel survived for 3 years or longer, compared with 13.5% who survived in the mitoxantrone group [15]. In addition, both arms saw similar trends in survival in men older than and younger than 65 years of age [15].

Another landmark Phase III trial, SWOG 9916, demonstrated an OS benefit with docetaxel and estramustine compared with mitoxantrone plus prednisone [3,16]. The median OS was 17.5 months in the docetaxel and estramustine group versus 15.6 months in the mitoxantrone plus prednisone group (p = 0.02), with a corresponding HR for death of 0.80 (95% CI: 0.67–0.97). Unlike the TAX 327 trial, there were no significant differences in self-reported pain relief between the two treatment groups. There were more AEs seen in the docetaxel group. The docetaxel and estramustine arm had higher rates of grade 3 or 4 neutropenic fevers, cardiovascular events, nausea and vomiting, metabolic disturbances and neurologic events.

Docetaxel-based chemotherapy was shown to prolong the median OS by 2–3 months when compared with mitoxantrone plus prednisone. Toxicities were greater in those patients treated with docetaxel with greater incidences of, for example, neutropenic fever, neutropenia, diarrhea, neuropathy and tearing. Estramustine has not been utilized in standard treatment with docetaxel secondary owing to concerns about its inferior toxicity profile without any clear benefit. It should be noted that the end point of OS may be confounded in both studies by crossover, so the median OS benefit may be larger in both trials.

In spite of this significant advancement in the treatment of mCRPC, all patients eventually discontinue docetaxel-based therapy owing to disease progression or toxicity. Although second-line hormonal therapies and mitoxantrone were commonly employed, there was no proven benefit and therefore numerous investigations explored the potential therapies after disease progression.

Platinum-based chemotherapy

Platinum-based chemotherapy has shown antitumor activity in prostate cancer as a single agent and in combination with other agents [17–20]. As noted by Oh *et al.*, platinum-based chemotherapy, initially alone and then in combination, has been evaluated in CRPC since the 1970s [21]. There have been small Phase II trials in the past decade that combined carboplatin with paclitaxel or docetaxel and estramustine with results showing PSA declines and objective responses. A multicenter CALGB Phase II trial in 40 patients with mCRPC utilized 5 days of estramustine, docetaxel 70 mg/m^2 and carboplatin with a target under the plasma concentration versus time curve of 5 every 3 weeks. PSA declines of greater than 50% were seen in 68% of evaluable patients. A total of 52% of patients had measurable responses (in 21 patients with measurable disease) [21].

Multiple clinical trials have explored combination regimens with platinum-based compounds and docetaxel. In a prospective Phase II study, Ross *et al.* investigated carboplatin plus docetaxel as second-line treatment in 34 men with docetaxel-refractory mCRPC [22]. Patients were treated with intravenous docetaxel 60 mg/m^2 plus carboplatin with an area under the curve of 4 once every 21 days. All patients had progressed during or within 45 days of completion of treatment with docetaxel. The median OS was 12.4 months with median progression-free survival (PFS) of 3 months. PSA declines of ≥50% were seen in 18% of the patients. A total of 56% of patients developed grade 3 leukopenia. Patients were more likely to respond to carboplatin plus docetaxel if they had previously responded to docetaxel.

Carboplatin plus paclitaxel after docetaxel in men with mCRPC was investigated in

a retrospective review of 25 patients from February 2000 to March 2008 [23]. All the patients received treatment with carboplatin and paclitaxel after treatment with docetaxel (carboplatin [area under the curve of 4–6] on day 1 plus paclitaxel 60–80 mg/m^2 on days 1, 8 and 21 on a 28-day cycle). A total of 88% of the patients were docetaxel refractory at the time of treatment. The median PFS was 12 weeks on carboplatin plus paclitaxel. There was no correlation found between response to docetaxel and response to carboplatin plus paclitaxel. Primary toxicities included anemia, leukopenia, fatigue and neuropathy.

Satraplatin is an oral platinum compound that was found to have preclinical activity in prostate cell lines resistant to taxanes, cisplatin and anthracyclines [24–26]. The SPARC study was a randomized Phase III trial conducted with the primary end points of PFS and OS [24]. Patients had stage D2 metastatic adenocarcinoma of the prostate with disease progression after one prior chemotherapy regimen. Not all patients had received docetaxel as first-line treatment. From September 2003 to January 2006, oral satraplatin 80 mg/m^2 or placebo was administered to 950 men once daily on days 1–5 of a 35-day cycle. Patients were randomly assigned in a 2:1 fashion. Both arms received prednisone 5 mg twice daily.

The primary end points were PFS and OS. PFS was a composite end point, which did not include an increase in PSA as a component. Components did include first occurrence of tumor progression, skeletal-related events (SREs), symptomatic progression or death. The median composite PFS was found to be greater with satraplatin at 11.1 weeks (95% CI: 10.3–12.3 weeks) versus 9.7 weeks with placebo. A 33% reduction in the risk of progression or death was seen with satraplatin (HR: 0.67; 95% CI: 0.57–0.77; $p < 0.001$). However, there was no difference in OS. As satraplatin did not demonstrate an OS benefit, it was not approved for second-line treatment in CRPC.

Platinum-based chemotherapy was also assessed in a Phase II study of carboplatin and etoposide in patients with anaplastic mCRPC with or without neuroendocrine differentiation. Fifty five patients were treated with carboplatin (area under the curve of 4) on day 1 and etoposide 100 mg/m^2 for 3 days repeated every 21 days. Patients had mCRPC with visceral metastases or any elevated neuroendocrine serum marker (neuron-specific enolase or chromogranin A). The response rates were low. In 46 patients with measurable disease, the objective response rate was 8.9%. The median OS was 9.6 months (95% CI: 8.7–12.7). There was one toxicity-related death, grade 3/4 neutropenia, thrombocytopenia, anemia, nausea and vomiting, as well as asthenia. Due to the high toxicity rate and low response rates, it was concluded that this combination would not be recommended in patients with anaplastic prostate cancer with or without neuroendocrine features [27].

Cabazitaxel

Cabazitaxel is a tubulin-binding taxane drug found to have cytotoxic activity in tumor models that are resistant to paclitaxel and docetaxel [28–30]. A Phase III trial of cabazitaxel for the treatment of mCRPC in men with disease progression during or after treatment with docetaxel (plus prednisone) was undertaken in 2007. A randomized open-label trial, TROPIC, was designed to assess OS in patients randomly assigned to cabazitaxel plus prednisone compared with mitoxantrone (plus prednisone) [28].

All patients received oral prednisone at 10 mg daily, and were randomized to receive either cabazitaxel 25 mg/m^2 intravenously over 1 h every 3 weeks or mitoxantrone at a dose of 12 mg/m^2 every 3 weeks. During cycle 1 of treatment, prophylactic G-CSF was not allowed, but was subsequently utilized at the physician's discretion after the first occurrence of neutropenia lasting 7 days or more, febrile neutropenia or neutropenia complicated by infections.

A total of 755 patients were randomly assigned to the two treatment groups between January 2007 and October 2008. Prior to this study, a median dose of 576.6 mg/m^2 of docetaxel had been received in the cabazitaxel treatment group and 529.2 mg/m^2 in the mitoxantrone group. The median survival was 15.1 months in the cabazitaxel arm compared with 12.7 months in the mitoxantrone arm (HR: 0.70; 95% CI: 0.59–0.83; $p < 0.0001$). The median PFS was also in favor of the cabazitaxel group, 2.8 versus 1.4 months (HR: 0.74; 95% CI: 0.64–0.86; $p < 0.0001$). Response rates for pain were similar in both groups. In addition, the median time to PSA progression was also superior in the cabazitaxel group (6.4 months) as compared with the mitoxantrone group (3.1 months).

More dose reductions and treatment delays were seen in the cabazitaxel group. Significant toxicities associated with cabazitaxel involved leukopenia, neutropenia, febrile neutropenia and thrombocytopenia. Seven patients died as a result of neutropenia and clinical consequences/sepsis compared with one patient in the mitoxantrone arm. The cabazitaxel arm had a higher risk of death within 30 days of the last treatment dose. Subgroup analyses revealed similar rates of survival in both the patients older than 65 years of age and patients younger than 65 years of age arms.

TROPIC was the first study to show an OS benefit for second-line chemotherapy in mCRPC (after docetaxel-based therapy). Preclinical data had shown that cabazitaxel was active in tumor cell lines that were resistant to taxanes, including docetaxel and paclitaxel. Some hypothesize that this is due to the lower affinity for the P-glycoprotein efflux pump [31]. Cabazitaxel was more toxic, with a higher rate of both neutropenia and febrile neutropenia. Indeed, prophylactic treatment with G-CSF has been recommended by the FDA label. Currently, a Phase III trial, FIRSTANA (NCT01308567), is investigating cabazitaxel versus docetaxel as first-line chemotherapy [102].

Taxane resistance

Treatment with taxanes is the only form of chemotherapy that has been shown to improve OS in men with mCRPC. In order to improve upon old therapies and develop new therapies, mechanisms of resistance to taxanes must be further evaluated. Taxanes work by binding β-tubulin, destabilizing microtubules during assembly and preventing microtubule depolymerization in the absence of GTP [31,32]. The androgen receptor (AR) has been implicated in the progression of prostate cancer when it translocates from the cytoplasm to the nucleus [33]. The AR then acts as a transcription factor. Taxanes bind β-tubulin and induce microtubule stabilization, which causes mitotic arrest and cell death. It has also been reported by Darshan *et al.* that taxanes affect AR signaling by inhibiting ligand-induced AR nuclear translocation and transcriptional activation of AR target genes [33]. The mechanisms of resistance are likely multifactorial. Alternative AR pathways and taxane-induced AR signal changes may lead to resistance [31]. The AR is an effective target for men with mCRPC who have progressed during or after docetaxel chemotherapy [34–36]. Decreased cellular drug accumulation can occur in cancer cells with *MDR1* gene expression via overexpression of the P-glycoprotein transporter, which increases efflux [37]. Overexpression of β-III-tubulin has been implicated in the progression to castration-resistant disease and has been shown to play a role in the resistance of tumor cells to docetaxel [38].

Multiple other mechanisms, such as mutations leading to changes in the microtubule binding site of taxanes, defects in the apoptotic pathways and possibly alerted androgen signaling cascades have been implicated in taxane resistance [31,39,40].

Combination therapy with docetaxel

Therapeutic combination therapy with docetaxel has been utilized to overcome taxane resistance in mCRPC. It is known that angiogenesis plays a crucial role in the processes of invasion, progression and metastases in prostrate cancer. In 1971, Judah Folkman first noted that tumors are unable to grow more than 2–3 mm in the absence of neovascularization [41]. Preclinical data have shown multiple pathways are involved in angiogenesis. One of the most studied pathways is that of VEGF family and its receptors and it has been found that prostate cancer cells express VEGF [42,43]. Increased microvessel density has been associated with increased expression of VEGF, and high blood and urine VEGF levels are associated with poorer survival rates in prostate cancer patients [44–46]. Bevacizumab is a humanized IgG1 monoclonal antibody targeting the VEGF ligand, which has been studied in combination with chemotherapeutic agents in prostate cancer [47].

The clinical benefit of chemotherapy and bevacizumab was addressed in CALGB 90401, which was a randomized Phase III study comparing docetaxel 75 mg/m^2, prednisone 5 mg twice daily and placebo with docetaxel 75 mg/m^2, prednisone 5 mg daily and bevacizumab 15 mg/kg in 1050 men with treatment-naive mCRPC [48]. Therapy was administered every 3 weeks. The primary end point was OS. PFS was 9.9 months in the bevacizumab arm versus 7.5 months in the docetaxel plus prednisone arm ($p < 0.0001$). There were also improvements in the PSA response rate in the bevacizumab group with a rate of 69.5 versus 57.9%.

However, no benefit was seen in OS. The median OS in the docetaxel, prednisone and bevacizumab arm was 22.6 versus 21.5 months in the docetaxel, prednisone and placebo arm (HR: 0.91; p = 0.18). There was a significantly higher morbidity with grade 3 neutropenia, hypertension and fatigue. In addition, death related to toxicity was 3.8% with bevacizumab versus 1.1%. Despite favorable Phase II studies, the CALGB 90401 trial was found to be a negative study.

Angiogenesis inhibitors continue to undergo further investigation in the treatment of prostate cancer. Aflibercept (VEGF Trap) is a humanized fusion protein that inhibits all forms of VEGF and PIGF [49]. Aflibercept inhibits VEGF binding to its receptors [16]. VENICE is an ongoing randomized Phase III trial with a primary end point of OS [103].

Thalidomide & derivatives

Thalidomide and its derivative lenalidomide have been studied in prostate cancer based on preclinical data suggesting thalidomide has antiangiogenic properties [50]. Thalidomide has been used by itself and along with bevacizumab in combination with docetaxel in prostate cancer [51]. Sixty patients with progressive mCRPC received docetaxel 75 mg/m^2 and bevacizumab 15 mg/kg on day 1 of a 21-day cycle with oral thalidomide (Celgene, Warren, NJ, USA) at 200 mg/day and prednisone at 10 mg/day. In addition, patients received enoxaparin at 1 mg/kg/day starting on day 1 [52]. PSA declines of greater than or equal to 50% were seen in 90% of patients. The median time to progression was 18.3 months and OS was 28.2 months. Adverse effects were common as all patients developed grade 3/4 neutropenia. Many patients required thalidomide dose reductions due to toxicities. Grade 2 thalidomide-related AEs included fatigue, constipation, peripheral neuropathy and depression. One death was possibly related to the use of bevacizumab secondary to myocardial infarction complicated by an aortic dissection. Attributable toxicities of bevacizumab included one grade 4 aortic dissection, grade 3 gastrointestinal perforation, grade 3/4 rectal fistula or ulcer, grade 4 nephrotic syndrome, grade 3/4 thrombosis and grade 3 bleeding. Based on these findings, the combination of bevacizumab and thalidomide with docetaxel may be more effective than either antiangiogenic agent alone with docetaxel, but also may increase toxicity.

Currently, the National Cancer Institute (NCI) is evaluating lenalidomide in a Phase II study in combination with docetaxel, bevacizumab and prednisone in metastatic chemotherapy-naive patients with mCRPC (NCT00942578; [104]). The activity seems comparable to the combination of thalidomide, docetaxel, bevacizumab and prednisone, with potentially a superior toxicity profile.

MAINSAIL was a double-blinded Phase III trial designed to evaluate the efficacy and safety of docetaxel and prednisone with or without lenalidomide in patients with CRPC. Unfortunately, in November 2011, the trial was discontinued as it was determined by the data monitoring committee that the combination of docetaxel and prednisone plus lenalidomide would not demonstrate a statistically significant treatment effect in OS versus docetaxel and prednisone plus placebo [105]. It should be noted that this trial did not include prophylactic G-CSF or enoxaparin in the experimental arm.

Immunotherapeutic agents

Vaccine therapy is an important therapeutic strategy in prostate cancer. The first immunotherapeutic agent approved in the setting of CRPC is sipuleucel-T, which is an autologous dendritic cell vaccine. Dendritic cells are harvested from a patient and fused to GM-CSF–prostatic acid phosphatase fusion protein. After 4 days, the cells are reinfused to stimulate an immune response. In a double-blind, placebo-controlled study, IMPACT, 512 men with mCRPC were randomly assigned to receive sipuleucel-T or placebo [53]. OS was the primary end point of the trial. Approximately 20% of patients had received prior chemotherapy. A median survival benefit of 4.1 months in favor of the sipuleucel-T arm (HR: 0.78; p = 0.032) was found. The 3-year survival was 30% with sipuleucel-T compared with 23% in the placebo arm. In future clinical trials, combinations of immunotherapeutic agents, such as sipuleucel-T, with chemotherapy should be considered. Pretreatment with vaccines might enhance the response to docetaxel-based chemotherapy [54]. The integration of vaccines into chemotherapy regimens has been accomplished without a negative impact on immune function [55]. In a randomized trial by Arlen *et al.* 28 patients

with metastatic androgen-independent prostate cancer were randomized to receive vaccine plus weekly docetaxel (n = 14) versus vaccine alone (n = 14). The vaccine was a recombinant vaccinia virus (rV) that expressed the *PSA* gene (rV-PSA) admixed with a rV that expresses the *B7.1* costimulatory gene (rV-B7.1). Patients also received sequential booster vaccinations with recombinant fowlpox virus containing the *PSA* gene. Immune responses for PSA-specific T cells were monitored. In this study, immunotherapy was administered with docetaxel without inhibiting specific T-cell responses and the median PFS on the docetaxel arm was 6.1 months after receiving the vaccine compared with 3.7 months with the same regimen in a historical control of patients treated with docetaxel [55].

Two randomized Phase III studies evaluated the allogeneic vaccine GVAX in combination with chemotherapy [56]. In the VITAL 1 trial, GVAX was compared with docetaxel plus prednisone in 626 patients with asymptomatic mCRPC with the primary end point of OS [57]. An interim analysis showed a <30% chance of achieving the primary end point and the study was terminated. The second study, VITAL 2, compared GVAX plus docetaxel with docetaxel plus prednisone in 408 patients with mCRPC [58]. An interim analysis revealed an excess of deaths in the docetaxel plus GVAX arm compared with the docetaxel plus prednisone arm (67 vs 47 deaths) and the study was terminated. There was a median survival of 12.2 versus 14.1 months in the docetaxel plus prednisone arm (HR: 1.70; p = 0.0076), and no significant toxicities in the docetaxel plus GVAX arm could explain the imbalance in deaths [58]. There is no role for GVAX in the treatment of prostate cancer in combination with chemotherapy.

Currently, three Phase III studies are underway in patients with CRPC using ipilimumab. Ipilimumab is a monoclonal antibody against CTLA4. CTLA4 is expressed on the surface of T-helper cells and downregulates T-cell responses, and has been shown to have activity in CRPC [48].

In the first trial, NCT01057810, ipilimumab is randomized against placebo in chemotherapy-naive patients [106]. In the second trial, ipilimumab is randomized against placebo in the postdocetaxel setting. Lastly, a study is assessing OS in patients with advanced prostate cancer treated with ipilimumab with radiotherapy versus radiotherapy alone. The results of these trials will be pivotal in assessing combination therapies with ipilimumab.

The abundance of new treatment options for men with advanced prostate cancer will challenge the role of immunotherapy in these patients. Future progress may rely on optimal combination and sequencing of various immunotherapies with androgen-directed approaches as well as with other standard prostate cancer therapies, an effort which is now just beginning.

Novel agents

New hormonal agents may be combined with taxane-based chemotherapy as treatment options for CRPC. Androgen signaling plays a role in the progression of CRPC. There is AR expression, which can be activated by low levels of testosterone, in approximately 90% of castration-resistant prostate tissue [59,60]. Rare mutations, overexpression and upregulation of the receptor can lead to an increase in intratumoral androgen concentrations [34]. Abiraterone acetate is a CYP17 inhibitor that blocks androgen synthesis by the adrenal gland and testes and from prostate cancer cells [61]. Phase I and II trials have investigated single-agent abiraterone or abiraterone plus low-dose steroids and found that antitumor activity occurs in both chemotherapy-naive and postchemotherapy patients [62,63]. Results of a Phase I clinical study of the combination of high-dose ketoconazole plus weekly docetaxel for mCRPC revealed a median OS of 36.8 months in chemotherapy-naive patients (n = 27). A median survival of 10.3 months was seen in patients who had previously progressed on docetaxel (n = 15) when docetaxel was reintroduced with ketoconazole. These data suggest that combining a taxane with a hormonal agent, such as abiraterone, may result in greater clinical benefits than taxane-based therapy alone [64]. Furthermore, docetaxel can be combined successfully with hormonal treatment in mCRPC and prolong taxane sensitivity [64].

In a Phase III trial, 1195 patients who had previously been treated with docetaxel were randomized to abiraterone 1000 mg daily plus prednisone 5 mg twice daily versus placebo plus prednisone 5 mg twice daily. OS was the primary end point of the study and was found to be longer in the abiraterone plus prednisone arm, 14.8 versus 10.9 months (HR: 0.65; 95% CI:

0.54–0.77; p < 0.001) [34]. The secondary end points of time to PSA progression, the PSA response rate and PFS all favored the abiraterone treatment arm. The rates of serious AEs were similar in the two treatment groups, but the abiraterone group had more mineralocorticoid-related events including fluid retention (2.3%), hypertension (1.3%), hypokalemia (3.8%) and cardiac disorders (4.1%). Based on these data, coupled with the Phase I and II studies, AR signaling has been validated as a hormonally mediated driver in CRPC.

MDV3100 is a pure AR antagonist that has been shown to be more potent than bicalutamide, flutamide and nilutamide, all of which have only partial agonist activity [35]. MDV3100 prevents translocation of the AR across the nuclear membrane. Further Phase III clinical trials, including the AFFIRM trial, are investigating MDV3100 in patients pre- and post-docetaxel chemotherapy. Data from the AFFIRM trial were presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium 2012 and showed an OS benefit for patients on the MDV3100 arm compared with placebo (18.4 vs 13.6 months; HR: 0.631; p < 0.001) [65].

Dasatinib is a tyrosine kinase inhibitor that inhibits the SRC family kinases and *in vitro* has shown activity in the decreased proliferation and migration of prostate cancer cells, including a hormone-refractory line [66,67]. A Phase I–II study of 46 patients combined dasatinib with docetaxel in men with CRPC [68]. In the Phase I portion of the study, 16 men were treated with dasatinib 50–120 mg once daily and docetaxel 60–75 mg/m^2 in 21-day cycles. Oral dasatinib was given on day 3 of cycle 1 and then continuously. In Phase II, 30 men received dasatinib 100 mg once daily and docetaxel 75 mg/m^2. Eight patients had been treated with docetaxel previously. Thirty seven patients (80%) had a decrease in PSA from baseline and 26 patients (57%) had a durable PSA response (sustained ≥50% decline for ≥6 weeks). A total of 60% (18 out of 30) of those with evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria had a partial response. In a bone marker assessment analysis, 33 out of 38 patients had decreases in urinary *N*-telopeptide levels. A total of 61% (28 patients) received single-agent dasatinib after docetaxel was discontinued and had stable disease for 1–12 months. Grade 3 AEs included alopecia, anemia, pleural effusion and peripheral sensory neuropathy. Overall, the combination of dasatinib and docetaxel was encouraging and was tolerated. Based on these data, a randomized Phase III study (NCT00744497) is in progress and will assess OS [107].

Another agent currently under investigation is OGX-011 (custirsen). OGX-011 is a second-generation phosphorothioate antisense molecule that inhibits clusterin expression [69]. Clusterin is a protein that has been associated with development of treatment resistance in prostate cancer and other cancers, when overexpressed [70]. Clusterin is stress activated and preclinical data have shown that knockdown of clusterin can enhance the effects of cytotoxic drugs, including docetaxel [70]. An open-label randomized Phase II study of OGX-011 evaluated the safety and efficacy of two second-line treatments for mCRPC [70]. Between July 2006 and April 2007, 45 patients were randomized to receive docetaxel plus prednisone plus OGX-011 (DPC) or mitoxantrone plus prednisone plus OGX-011 (MPC). There were 20 patients in the DPC arm and 22 in the MPC arm who received treatment. More patients in the MPC arm (64%) had progressed on first-line therapy than in the DPC arm (40%). The median number of treatment cycles of docetaxel prior to study entry was ten cycles in each arm. Grade 3 or 4 AEs were similar in the two arms and included fatigue and lymphopenia. On the DPC arm, 60% of patients had a grade 3 or higher AEs compared with 73% on the MPC arm. The most common grade 3 or 4 AEs were fatigue and lymphopenia. In the DPC arm, OS was 15.8 months, median time to pain progression was 10 months and three out of 13 patients with evaluable disease had a partial response. PSA declines of 90% or more were seen in four patients, and declines of 50% or more in eight patients. In the MPC arm, the OS was 11.5 months, time to pain progression was 5.2 months and no objective responses were seen. PSA declines of 50% or more and 30% or more occurred in six and seven patients, respectively. The relationship between serum clusterin levels and survival was an exploratory end point in the study and those with low serum clusterin levels were associated with a 70% reduction in the hazard of death at the start of the serum response (p < 0.001). Treatment with either combination was tolerated and warrants

further studies. Two Phase III studies are currently underway, one evaluating OS, the other evaluating pain palliation, and both evaluating serum clusterin levels as a predictive biomarker for survival.

Chemotherapy may also be combined with bone-seeking radiopharmaceuticals in order to evaluate for synergy that would prolong OS [71]. ^{153}Sm ethylenediamine tetramethylene phosphonate (^{153}Sm-EDTMP) and ^{89}Sr deliver radiation to areas of newly remodeled bone as in osteoblastic bone metastases [72]. Both ^{153}Sm and ^{89}Sr are β-radiation-emitting isotopes that are approved for use for palliative treatment of bone pain in mCRPC. Multiple studies have reported significant improvements in pain associated with mild hematological toxicities with ^{153}Sm.

A Phase I study of 28 patients combined ^{153}Sm-EDTMP with docetaxel. The combination was well tolerated and 58% of patients had a ≥50% PSA decline. Patients previously treated with a taxane (n = 8) or thought to be taxane refractory (n = 4) also had PSA declines of ≥50% [73].

A Phase II study conducted at MD Anderson Cancer Center (Houston, TX, USA) combined doxorubicin with ^{89}Sr in 103 patients with chemosensitive CRPC. The patients initially received two or three cycles of induction chemotherapy. Patients were treated with weekly doxorubicin 20 mg/m^2 in weeks 1, 3 and 5 with ketoconazole 400 mg by mouth three-times daily for 7 days. In weeks 2, 4 and 6, they were treated with vinblastine 4 mg/m^2 weekly with estramustine 140 mg by mouth three-times daily for 7 days. Subsequently, 72 patients who were clinically stable or had responding disease were randomized to receive doxorubicin with or without ^{89}Sr every week for 6 weeks. An OS benefit was seen in the combination arm compared with the doxorubicin alone arm (28 vs 17 months; HR: 3.76; 95% CI: 1.44–5.29; p = 0.0014) [74]. This was the first study to show an OS benefit with ^{89}Sr utilized as consolidative therapy with doxorubicin.

In a Phase I and II study, gemcitabine was given in combination with ^{89}Sr to patients with CRPC with painful bone metastases [75]. Fifteen patients were treated on a 12-week course and received gemcitabine (600 mg/m^2 or 800 mg/m^2) on days 1, 8, 15, 43, 50 and 57. A single dose of ^{89}Sr (55 μCi/kg) was given on day 8. The maximum tolerated dose of gemcitabine was determined to be 800 mg/m^2. The primary end point in the Phase II portion of the study was reduction in serum PSA. The primary AEs included thrombocytopenia and neutropenia. There were no responses and the study was terminated, but six patients (40%) had stable disease.

^{223}Ra (Alpharadin®) is an α-radiation-emitting isotope that has been studied in CRPC patients with symptomatic bone metastases [76]. In a Phase II, placebo-controlled study, 64 patients were randomized to receive four intravenous injections of ^{223}Ra (50 kBq/kg) or placebo every 4 weeks [77]. All patients received external-beam radiation. The primary end points of the trial were change in bone alkaline phosphatase and time to SREs. Secondary end points were toxic effects, time to PSA progression and OS. ^{223}Ra treatment was well tolerated with minimal hematologic toxic effects, which is advantageous in comparison to β-emitting isotopes. The median change in bone alkaline phosphatase from baseline to 4 weeks after the last injection was -65.6% (95% CI: -69.5 to -57.7) in the treatment group versus 9.3% (95% CI: 3.8–60.9) in the placebo group ($p < 0.001$; Wilcoxon ranked-sum test). The ^{223}Ra group also had improved PFS (26 vs 8 weeks; p = 0.048) and OS (65.3 vs 46.4 weeks; p = 0.066). The HR for OS (adjusted) was 2.12 (95% CI: 1.13–3.98; p = 0.020; Cox regression). Time to SREs and pain control were not statistically significant between the two groups.

The results of an interim analysis for the Phase III ALSYMPCA trial were presented at the European Society for Medical Oncology–European Cancer Organization (ESMO–ECCO) European Multidisciplinary Cancer Congress. The primary end point of the trial is OS and secondary end points include time to occurrence of SREs, changes and time to progression in PSA, QOL and health economics [78]. A total of 922 patients were randomly assigned in a 2:1 fashion to ^{223}Ra or placebo. A total of 615 patients received ^{223}Ra and 307 patients received placebo. An OS benefit was seen in the ^{223}Ra group (14 vs 11.2 months; HR: 0.695; 95% CI: 0.552–0.875; p = 0.00185). Again, the toxic effects were minimal with grade 3/4 neutropenia of 1.8% in the ^{223}Ra group versus 0.8% in the placebo group. The combination of ^{223}Ra with chemotherapeutic agents is a novel

treatment option and no doubt will be explored in the future.

Unfortunately, there have been negative combination trials such as the combination trial with AT-101. AT-101 is an oral inhibitor of the Bcl-2 family, which has been found to have activity in mCRPC. In a Phase II trial, 221 men with mCRPC were randomized to receive docetaxel plus prednisone combined with either AT-101 or placebo [79]. Patients received docetaxel 75 mg/m^2 on day 1 and prednisone 5 mg twice daily orally every 21 days with AT-101 40 mg or placebo twice daily orally on days 1–3. The primary end point was OS, but there were no statistically significant differences in the primary or secondary end points. The median OS for AT-101 plus docetaxel and prednisone was 18.1 versus 17.8 months for the placebo group (HR: 1.07; 95% CI: 0.72–1.55; p = 0.63). Future trials may incorporate AT-101 in higher-risk patients in whom benefit may be seen.

Many new targeted agents are currently undergoing investigation and may one day be utilized with chemotherapy. TAK-700 is an oral 17,20 lyase inhibitor which has shown PSA responses in a Phase I trial at doses of 300 mg or greater twice daily [80]. TAK-700 is undergoing further evaluation in two ongoing Phase III trials. Cabozantinib (XL-184) is an oral targeted agent that inhibits c-MET and VEGF receptor tyrosine kinases. In a Phase II discontinuation study by Hussain *et al.*, patients were randomly assigned to receive cabozantinib or placebo [81]. There were 171 assessable patients with 43% treated with prior docetaxel and 87% with bone metastases. At 12 weeks, 79% of patients had stable disease and 4% had a tumor response. One hundred and eight patients had lesions upon bone scan with 75% of patients having complete or partial resolution of lesions and 21% having stable bone scans. The median PFS was longer with cabozantinib (21 vs 6 weeks; HR: 0.13; p = 0.0007). A Phase III trial is currently planned.

The results of these clinical trials may herald a new approach in the treatment of CRPC as they may potentially enhance the treatment with taxane-based chemotherapy alone. In addition, the sequence of treatment options with chemotherapy needs further investigation.

Conclusion & future perspective

Taxane-based chemotherapy remains the first-line treatment in mCRPC. Over the past decade, the role of chemotherapy has evolved with the OS survival benefit seen with docetaxel plus prednisone. Second-line treatment, after progression on or after docetaxel, was approved in the form of cabazitaxel. Antiangiogenic agents, such as bevacizumab, have not shown a survival benefit at this time, but other agents and combinations warrant further study. In order to potentiate and elongate the effects of taxane-based therapy, mechanisms of taxane resistance need to be analyzed. The future of chemotherapy may be in taxane-based combinations, in particular with hormonal agents, which target the AR or other novel molecules. Individualized targeted therapies in combination with chemotherapeutic agents will be at the forefront of treatment options in the future.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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