Systemic therapy after first-line docetaxel in metastatic castration-resistant prostate cancer

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Purpose of review

There is an urgent need for systemic treatment options for patients with castration-resistant prostate cancer who have progressed after receiving first-line docetaxel chemotherapy. The purpose of this article is to review recent developments in this area.

Recent findings

Retreatment with docetaxel has been employed with evidence of activity in selected populations. Mitoxantrone, the previous first-line standard based on its palliative effect, has also been used with clinical responses observed; however, the symptom benefit in this setting has not been established. Several classes of cytotoxic agents have been tested including platinum agents (satraplatin), epothilones (ixabepilone and patupilone) and taxanes (XRP-6258). A number of targeted therapies have also been clinically evaluated including inhibitors of cytoprotective chaperones (OGX-011) and the vascular endothelial growth factor receptor (sorafenib, sunitinib, and cediranib). An area generating great interest has been the development of agents that target the androgen receptor axis more effectively (MDV3100 and abiraterone) with encouraging early phase trial results.

Summary

There is no accepted standard systemic treatment for patients with castration resistant prostate cancer and progressive disease after docetaxel. Novel agents are in phase II and III clinical testing in this setting.

Keywords

antineoplastic agents, prostate cancer, second-line therapy

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Introduction

Castration-resistant prostate cancer (CRPC), also termed hormone refractory prostate cancer (HRPC), is defined as a rising serum prostate-specific antigen (PSA) in the face of castrate levels of testosterone. CRPC is an incurable condition projected to cause almost 30 000 deaths in America alone in 2008 [1]. Significant morbidity in the form of pain and fatigue are associated with this condition and the goals of treatment emphasize symptom control in addition to prolongation of life.

The current first-line standard of care for patients with symptomatic or progressive disease is docetaxel-based chemotherapy. This follows the publication of two phase III randomized trials [2,3], which demonstrated a survival advantage of docetaxel-based chemotherapy over the previous standard treatment being mitoxantrone [4]. Symptomatic and quality of life benefits were also observed to be associated with docetaxel.

With the identification of effective first-line therapy for CRPC, there is now a need for further treatment options after docetaxel. The average duration of treatment was 6–7 months in these studies and with a median survival of 18.2 months, progression-free survival (PFS) of 6.3 months and median time to pain progression of 3.5–5.6 months; there still remains significant opportunity for additional therapies. To date, for patients with progressive disease after first-line docetaxel, there is no accepted standard of treatment. This review will describe the most recent developments in this field and the novel therapeutics currently in clinical trials for patients with disease progression after or during docetaxel chemotherapy.

Cytotoxic chemotherapy

Given the paucity of current treatment options in the second-line setting, docetaxel is commonly reused or mitoxantrone chemotherapy. Clinical trials of satraplatin,

epothilones and newer taxane agents are ongoing, and are highlighted here.

Retreatment with docetaxel

Retreatment with docetaxel has been a treatment strategy that has been evaluated. Chemo naïve patients who achieved a PSA of less than 4 ng/ml and met the criteria for PSA response during first-line docetaxel treatment [5] were invited to enroll in a study of intermittent docetaxel rechallenge on progression [6•]. Patients recommenced docetaxel when their PSA increased by 50% from post chemotherapy nadir and was more than 2 ng/ml or if they had other evidence of progression. Of the 250 patients who commenced first-line treatment, 56 were eligible with 45 consenting to participate and 33 evaluable for response. Of the patients who resumed docetaxel treatment after a 'chemotherapy holiday' of mean 18 weeks, 45.5% patients responded with a PSA decline of at least 50% and 45.5% met criteria for stable PSA for at least 12 weeks. This study indicates that retreatment with docetaxel could result in continued responses; however, this was a highly selected population (33 of the initial 250 patients). All had a prior excellent response to docetaxel, with a low PSA and short intervals between courses of treatment. They also had better prognostic indices compared with those not eligible for intermittent treatment.

A retrospective review [7•] of the baseline characteristics and outcomes of patients retreated with docetaxel after first-line use has recently been reported. From 393 patients receiving first-line docetaxel, 25 (6%) patients were retreated with docetaxel with a median interval of 11.8 months between end of first-line and commencement of second-line treatment. PSA declines of at least 30 and 50% occurred in 13 (52%) and 8 (32%) patients, respectively. Median overall survival was 9.6 months from the commencement of second-line docetaxel. Another retrospective review of patients retreated with second-line single agent docetaxel reported similar response rates [8•] for patients who responded to first-line docetaxel with 11 of 26 patients (42%) having had a PSA decline of at least 50%.

Thus, docetaxel re-treatment is a reasonable option in a selected subgroup of patients who have previously tolerated first-line therapy. Patients who appear to benefit include those who have had a previous response to treatment and have few adverse prognostic markers at the initiation of treatment.

Mitoxantrone

Being the previous standard of care prior to 2004, mitoxantrone has been utilized post docetaxel. Retrospective studies have reported modest activity with PSA response rates in 10–20% of patients in this setting [9,10]. Retrospective crossover results of the practice changing TAX 327 trial [3] were reported in abstract form in 2007 [11•]. Of 45 patients with data available who received mitoxantrone after docetaxel, a PSA response (≥50% reduction) occurred in only 9%.

The low level of activity of mitoxantrone in this setting is also highlighted in two randomized phase II trials with mitoxantrone as the control arm. Patients progressing within 60 days of docetaxel treatment were randomized to either mitoxantrone or ixabepilone [12•]. The mitoxantrone arm induced a PSA response in 20% of patients, with a median treatment duration of 2.3 months, a 63% rate of grade 3 and 4 neutropenia and median survival of 9.8 months. Similarly, mitoxantrone was the control arm in an abstract presented in 2007 [13]. Patients progressing during or within 90 days of docetaxel treatment were randomized to one of three treatment arms. Results of the mitoxantrone arm reported a median number of two cycles being delivered, with a time to progression of 1.1 months. No PSA responses were seen and the grade 3 and 4 febrile neutropenia rate was 31%.

From these data, although mitoxantrone has been observed to induce PSA responses ranging from 0 to 20% in the post docetaxel setting, time to progression is generally brief and toxicity is clinically significant with no clear data on any palliative effect. Mitoxantrone therefore should only be considered in this patient population if active treatment is preferred in symptomatic patients when clinical trials are not an option.

Satraplatin

Satraplatin is an orally bioavailable platinum compound which in phase II studies demonstrated activity and an acceptable toxicity profile in patients with CRPC. A phase III study (SPARC) was conducted comparing satraplatin in combination with prednisone vs. placebo and prednisone [14•]. The study's coprimary end points were PFS and overall survival. PFS was determined via evidence of radiological progression, symptomatic progression or death and not by PSA increases. Nine hundred and fifty patients with CRPC progressing through a minimum of two courses of one prior cytotoxic chemotherapy (51% had received prior docetaxel) were randomized in a 2 : 1 ratio. The satraplatin arm resulted in significantly better PSA response (25.4 vs. 12.2%; $P < 0.001$), pain response (24.2 vs. 13.8%; $P < 0.005$) and time to pain progression (66.1 vs. 22.3 weeks; $P < 0.001$). Median PFS was 11 vs. 9.7 weeks, with a 33% reduction in the overall risk of disease progression [hazard ratio = 0.67; 95% confidence interval (CI) 0.57–0.77; $P < 0.001$]. Although statistically significant, the clinical significance of this difference in PFS is open to interpretation. Additionally, overall survival was subsequently shown to not differ between the two arms

(61.3 vs. 61.4 weeks, hazard ratio = 0.97, 95% CI 0.83–1.13, $P = 0.80$).

Epothilones

Epothilones, which include epothilones A, B, and D, were originally identified as metabolites secreted by the myxobacterium *Sorangium cellulosum*. Like taxanes, the principal mechanism of anticancer activity is through microtubule stabilization resulting in mitotic arrest at the G2 and M phase of the cell cycle and eventual apoptosis. Despite a similar mode of action, preclinical studies have shown that the epothilones are more potent inducers of tubulin polymerization than paclitaxel and inhibit cell growth across a broad panel of taxane-sensitive and taxane-resistant human tumor cell lines [15]. Epothilone B (patupilone, EPO906; Novartis, Basel, Switzerland), its semisynthetic derivative ixabepilone (BMS-247550; Bristol-Myers-Squibb, New York, USA), and epothilone D (KOS-862; Kosan Biosciences, California, USA) have been studied in the postdocetaxel setting.

Ixabepilone was investigated as second-line treatment in 82 patients with metastatic prostate cancer unresponsive to paclitaxel, docetaxel or hormone therapy [12•]. This multicenter trial randomized patients to either ixabepilone 35 mg/m^2 every 3 weeks or mitoxantrone 14 mg/m^2 and prednisone 5 mg twice daily. Median survival was similar in both groups (10.4 months with ixabepilone and 9.8 months with mitoxantrone and prednisone) and PSA responses were observed in 17% of the ixabepilone-treated patients and in 20% of mitoxantrone-treated patients. Neutropenia was the most common grade 3 and 4 toxicity occurring in 54% of ixabepilone and 63% of mitoxantrone patients.

A phase II trial of weekly ixabepilone has been reported in abstract form [16•]. Of the 69 patients enrolled, 37 of these had prior exposure to taxanes. Patients were treated with intravenous (i.v.) ixabepilone 20 mg/m^2 weekly for 3 of every 4 weeks. Grade 3 and 4 neutropenia was observed in five out of 37 (14%) of the prior taxane-treated patients. Neuropathy and fatigue were the other most common grade 3 and 4 toxicities, both occurring in five out of 37 patients previously treated with taxane. PSA and objective responses were observed in 22 and 27% of patients, respectively.

Epothilone D has been investigated in a phase II trial following docetaxel treatment. Beer *et al.* [17•] reported on 38 patients treated with 100 mg/m^2 i.v. weekly for 3 of every 4 weeks. PSA response rates were low at 5.3 and 73% of patients required dose reduction or cessation of treatment because of toxicity.

A phase II study of patupilone administered weekly in 37 patients has been reported in abstract form [18]. Twenty-nine of these patients had received a maximum of one prior chemotherapy regimen. PSA values were available in 30 patients, and eight (22%) had a partial PSA response. The two most common side effects were diarrhea, with 19% of patients having grade 3 and 4 symptoms and grade 1 and 2 peripheral neuropathy in 19%.

Another multicenter phase II study with patupilone was recently reported [19••] with patupilone administered on a once every 3-week schedule as preclinical data indicated that higher less frequent dosing was more efficacious with potentially reduced toxicity. In this trial, patients had to have progressive disease during or within 6 months of docetaxel. At the time of reporting, data were available for 40 patients who had received a median of four cycles of treatment and 38 patients were evaluable for PSA response. PSA declines of at least 30 and 50% were seen in 20 out of 38 (53%) and 18 out of 38 (47%) patients. No grade 3 and 4 hematological toxicities were observed and grade 3 and 4 adverse events at 8 mg/m^2 dosing included fatigue (21%) and diarrhea (12%).

Despite much initial enthusiasm for the epothilones, in this chemotherapy-pretreated population both ixabepilone and KOS-862 have resulted in significant toxicity and a low level of activity. Patupilone administered on a once every 3-week schedule has promise and mature data are awaited from the ongoing phase II study.

Taxanes

XRP2658 (Sanofi-Aventis, Paris, France) is a semisynthetic taxoid compound with low affinity for the P-glycoprotein drug efflux transporter and cytotoxic in cell lines with acquired resistance to paclitaxel or docetaxel [20]. A phase II study of XRP6258 was conducted in patients with docetaxel refractory metastatic breast cancer and an objective response rate of 14% was observed. Two patients achieving a complete response with a median response duration of 7.6 months.

A phase II trial with XRP6258 has not been performed in patients with CRPC; however, given its activity in the docetaxel refractory setting described above, this agent is currently being investigated in a phase III multicenter, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate resistant metastatic prostate cancer previously treated with docetaxel-containing treatment. The aim is to recruit 720 patients with a projected completion date of May 2010.

Targeted therapy

A number of targeted agents have been tested in patients with CRPC in the postdocetaxel setting. This includes agents that target cytoprotective chaperone proteins,

angiogenesis through the vascular endothelial growth factor pathway, apoptosis associated proteins, mTOR and the androgen receptor axis. Several of these agents are entering randomized clinical testing and are highlighted here.

Custirsen

Clusterin is a cytoprotective chaperone protein that promotes cell survival and confers broad-spectrum treatment resistance. Clusterin is overexpressed in prostate cancer and expression increases after therapeutic interventions [21]. Custirsen (OGX-011; Oncogenex Technologies Inc., Vancouver, Canada) is a 2′-methoxyethyl-modified phosphorothioate antisense oligonucleotide that is complementary to clusterin mRNA and inhibits clusterin expression *in vitro*, *in vivo*, and in humans [22]. Recently published preclinical work supports the principle that custirsen can lead to the resensitization of previously docetaxel-resistant prostate cancer cells [23•].

A phase II trial evaluating the safety and efficacy of custirsen in combination with either docetaxel or mitoxantrone as second-line treatment for patients with CRPC has been recently presented [24••]. Eligible patients had progressed during or within 6 months of docetaxel treatment. All patients received 640 mg i.v. weekly of custirsen and patients randomized to docetaxel and prednisone or mitoxantrone and prednisone. Forty-two patients received at least one cycle on study. Sixteen patients (38%) had prior progressive disease whilst receiving first-line docetaxel and therefore this was a relatively refractory population. In the docetaxel and mitoxantrone arms, PSA declines of at least 50% were seen in 60 and 27% of patients and pain response in 67 and 50%, respectively. A randomized study of docetaxel with or without custirsen is planned in this patient group.

Vascular endothelial growth factor receptor targeting agents

Vascular endothelial growth factor and vascular endothelial growth factor receptor (VEGF/VEGFR) activation has been implicated in the androgen-independent progression of prostate cancer. Elevation of VEGF has been correlated with poor prognosis and disease progression [25] and inhibition of the VEGF and VEGFR pathways in experimental models induces an antitumor effect. Sorafenib and sunitinib are orally administered agents that potently inhibit the tyrosine kinase activity of VEGFR, as well as a number of other kinases. Both agents are already approved for use in metastatic renal cell cancer.

Dahut *et al.* [26••] have published the results of the first stage of a two-stage phase II trial evaluating sorafenib in 22 patients, 59% of whom had received one prior chemotherapy treatment. The primary objective was to determine if sorafenib was associated with a 4-month probability of PFS (including PSA progression) in 50% of patients. There was little concordance amongst the progression criteria, with 21 out of 22 patients reported as progressing; however, 13 out of 21 progressed on PSA criteria alone with no evidence of clinical or radiological progression. Interestingly, two patients who met criteria for PSA progression were found to have reduction of bone metastatic lesions at the time of PSA progression. Subsequent in-vitro studies have suggested a sorafenib-induced increase in PSA independent of its cytotoxic effects and thus PSA may not be reflective of disease progression with this class of agents. The trial was amended to remove PSA increase as a progression criteria and the second stage of this trial has accrued.

A study investigating sunitinib has been recently presented [27•]. This trial used clinical and radiological determinants of progression, with the primary objective being to determine if sunitinib therapy was associated with a clinical PFS of 12 weeks in more than 30% of patients. All patients had received one or two prior chemotherapies including docetaxel. A 12-week PFS was attained in 78.9% of patients. Forty-seven percent of patients discontinued therapy because of toxicity and there were two possibly drug-related deaths. A phase III study has been initiated which will randomize patients with CRPC progressing after docetaxel to receive either sunitinib or placebo in a 2 : 1 fashion. The primary endpoint is overall survival and a planned 819 patients are to be enrolled.

Targeting the androgen receptor

The term 'HRPC' has been replaced with the term 'castrate resistant' as current preclinical and clinical data illustrate that the androgen receptor (AR) is expressed and continues to mediate androgen signaling even after failure of androgen ablation therapy [28]. The mechanisms of high expression and continued AR activation are multifactorial and result in several potential targets for inducing treatment responses via manipulation of AR activation [29]. Two new agents in clinical trials are targeting various mechanisms of AR activation: MDV3100 (Medivation Inc., San Franciso, California, USA) and abiraterone acetate (Couger Biotechnology Inc., Los Angeles, California, USA).

MDV3100 is a potent novel small AR antagonist that prevents nuclear translocation and DNA binding of AR, and posses no agonistic activity. A first-in-men, multicenter phase I and II dose-escalation study was recently reported and demonstrates encouraging clinical results. Treatment has been well tolerated and early results indicate that 13 of 14 patients followed for more than 4 weeks have had PSA declines including patients previously treated with docetaxel. The trial is ongoing and continues to accrue [30••].

Abiraterone acetate is an orally available inhibitor of 17α-hydroxylase and $C_{17,20}$-lyase, both of which are necessary for androgen synthesis from cholesterol precursors. Data from several ongoing phase II trials have been very persuasive with a high rate of response occurring in patients with progression after first-line docetaxel therapy. In a recent presentation of results on 28 patients who had previously received docetaxel, 40% of patients were noted to have a PSA decline of at least 50% [31••].

Of 18 patients with measurable disease, four (22%) had a partial response. Eleven patients remained on therapy for more than 6 months and the median time to progression was an impressive 167 days. Treatment was well tolerated with only grade 1–2 adverse events. A randomized, double-blind, placebo-controlled trial of abiraterone and prednisone has been initiated. Patients are being randomized 2:1 in favor of abiraterone with a planned 1158 patients to be enrolled. The trial is powered to detect a difference in median overall survival of 15 months in the abiraterone group vs. 13 months in the placebo group (hazard ratio = 0.80).

Conclusion

There is no accepted standard systemic therapy for patients who progress after docetaxel therapy. In the absence of proven therapy, foremost consideration needs to be given to palliation of symptoms through adequate analgesia and radiotherapy. Docetaxel retreatment may be an option for a subset of patients who have tolerated and responded to first-line docetaxel therapy. Mitoxantrone has become a de-facto second-line treatment but its benefit has not been clearly demonstrated in this setting. A number of chemotherapy and targeted therapy agents are being tested in phase II and III clinical trials and their results are eagerly awaited.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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