

Castrate-resistant prostate cancer: the right targets and combinations

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Metastatic prostate cancer is the second leading cause of death in the USA. There are currently limited chemotherapeutic agents in the treatment of castrate-resistant prostate cancer (CRPC). Currently, docetaxel is the only approved chemotherapeutic agent that has been able to show a survival advantage. There have been several trials of other chemotherapeutics that have not been able to show a survival advantage, and this led to greater toxicity. As different molecular targets are discovered, there are opportunities for targeted therapies for metastatic prostate cancer. In addition, exploration of targeted combination therapies has led to further advances. This article reviews some of the recent targets and trials being used in combination therapy for CRPC.

Prostate cancer is the most common cancer in males and the second leading cause of death in the USA [1]. Whereas androgen ablation therapy is an effective initial modality in patients with metastatic disease, androgen independence and progression of disease eventually occurs [2,3]. Chemotherapy has been increasingly used for metastatic prostate cancer over the past decade. Two regimens that use docetaxel in combination with either prednisone or estramustine have shown an increased survival compared with mitoxantrone and prednisone [4,5]. There has been extensive testing of different chemotherapeutic regimens as single agents and in combinations with generally disappointing results. The limited armamentarium and toxicities associated with chemotherapy has resulted in exploration of molecularly targeted agents to treat metastatic prostate cancer.

Anti-angiogenesis therapy

The discovery of elevated levels of VEGF in prostate cancer has prompted the exploration of anti-angiogenic therapies. Bevacizumab is an anti-angiogenic monoclonal antibody targeted against VEGF that is approved in combination therapy for several different tumor types. In prostate cancer, bevacizumab has been evaluated in combination with docetaxel and estramustine. Picus *et al.* reported a Phase II trial that combined bevacizumab with estramustine and docetaxel in 79 men with castrate-resistant prostate cancer (CRPC). The combination of docetaxel, estramustine and bevacizumab resulted in a prostate-specific antigen (PSA) decline of greater than 50% in 81% of patients, a median time to disease progression of

9.7 months and an overall median survival of 21 months [6]. Currently, Cancer and Leukemia Group B (CALGB) 90401 has an ongoing trial that is comparing docetaxel and prednisone with or without bevacizumab. The primary end point is overall survival (OS).

Immunomodulatory and anti-angiogenic agents such as thalidomide and lenalidomide are being explored alone and in combination with chemotherapeutic agents. A Phase II trial randomized 75 chemotherapy-naïve CRPC patients to receive 30-mg/m² weekly docetaxel for 3 consecutive weeks followed by a 1-week rest period or docetaxel at the same dose and schedule plus thalidomide 200 mg orally each day. After a follow-up period of 26.4 months, the percentage of patients with a greater than 50% decline of PSA was higher in the combination group (51% vs 37% in the single-agent docetaxel group). Median progression-free survival (PFS) was 5.9 months in the combination arm and 3.7 months in the docetaxel arm. The median survival in the docetaxel group was 14.7 months and 28.9 months in the combined group. It should be noted that although the study was not powered to detect a survival difference, the addition of thalidomide nearly doubled the median survival in patients with metastatic CRPC [7]. The most frequent toxicities were constipation, neuropathy and fatigue and were generally mild. There was an increased risk of venous thromboembolism (VTE) in the combination arm, with nine of 47 patients developing a VTE as compared with none in the docetaxel alone group. After this increased risk of VTE was noted, prophylactic enoxaprin was added to the combination arm and no additional VTEs were noted.

Keywords: anti-angiogenic therapy, antisense therapeutics, castrate resistant prostate cancer, combination therapy, targeted therapy, tyrosine kinase inhibitor

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Preclinical data indicated that thalidomide and bevacizumab target different angiogenic factors, leading to a trial of bevacizumab, docetaxel, thalidomide and prednisone at the NIH Clinical Center by our group. A total of 54 of 60 patients have been enrolled. The median number of treatment cycles to date is 12 (2–40). The toxicities that have been noted are: febrile neutropenia (5/54), syncope (4/54), colon perforation or fistula (2/54), grade 3 bleeding (2/54) and thrombosis (3/54). In addition, patients had neuropathy (36/50), fatigue or somnolence (14/50) and constipation (all patients required initial intervention, but none were grade 3 or 4). In total, 46 patients (87%) had PSA declines of greater than 50%, with median greater than 50% PSA-duration of 11 cycles (0 to approximately 38). A total of five patients had PSA declines of 10–40%, and two patients had no decline in PSA. A total of 38 patients (72%) had a greater than 80% PSA decline. A total of 29 patients with measurable disease were evaluable: 1 complete response (CR), 14 partial response (PR), 13 stable disease (SD), and 1 progressive disease (PD), with 52% ORR.

A Phase I trial ($n = 19$) that assessed the tolerability of lenalidomide (10–25 mg/day for days 1–14) in combination with docetaxel (60 or 75 mg/m² on day 1 of 21) in metastatic CRPC in patients who had less than two prior regimens found the combination to be well tolerated [8]. The toxicities consisted of grade 3 neutropenia (3) and grade 2 neuropathy (1) and fatigue (1). Nine patients (47.4%) have had a greater than 50% decline in serum PSA. A total of 13 patients had measurable disease, five (38.5%) achieved a PR and seven patients (53.9%) had stable disease. The maximum tolerated dose (MTD) has not been reached at the time of the publication.

Cediranib, an orally available small molecule, is a potent inhibitor of receptor tyrosine kinases, which influence VEGF. Cediranib has been shown to inhibit VEGF signaling by inhibiting KDR and Flt-1 kinase activity. A Phase I trial in refractory prostate cancer patients (26) was conducted and found to have a MTD of 20 mg. Dose-limiting toxicities occurred in the 30 mg dose and consisted of fatigue and muscle weakness [9]. A preliminary Phase II study is being conducted by our group at the NIH with a total of 16 patients enrolled to date with a total accrual to 35 evaluable patients. There have been decreases in lymph node metastases as well as in lung, liver and bone lesions. A total of nine patients have had disease progression, and seven remain on trial (1–10 months). PSA levels have

not corresponded well with imaging responses. Adverse events have been similar to other drugs in this class and have included hypertension, dysphonia, nausea and fatigue. The following grade 3 toxicities occurred: vomiting (1), prolonged QTc interval (1) and muscle weakness (1). Currently, there is an ongoing trial using docetaxel and prednisone with or without cediranib in patients who are castrate-resistant prostate cancer using a primary end point of 6-month PFS.

Calcitriol

Vitamin D and its analogues have been known to have growth and differentiating potential. In addition, there is evidence to suggest that low serum levels of 1,25 dihydroxyvitamin D (calcitriol) may be a risk factor for prostate cancer. Calcitriol may help to potentiate the effects of mitoxantrone and docetaxel. An early study that was conducted showed that 37 men who progressed after androgen therapy were given weekly therapy with calcitriol (0.5 mcg/kg) prior to docetaxel. There was a PSA decrease of 75% in 22 patients and eight of 15 patients with measurable disease had a partial response. The median survival was 19.5 months [10].

This evidence lead to a multicenter randomized trial of 250 patients (AIPC Study of Calcitriol Enhancing Taxotere [ASCENT] 1) who had progressed after hormonal therapy that compared weekly docetaxel (36 mg/m² for 3 of 4 weeks) with or without calcitriol. The calcitriol or placebo was given the day before docetaxel. The median follow-up was 18 months, and no significant differences in both PSA response and tissue response were observed [11]. A Phase III trial using survival as an end point was closed early due to increased deaths in the combination arm [12].

Endothelin-A inhibitors

Endothelin-1 and the receptor ET-A have shown paracrine effects as well as growth and increased levels in progressive disease. Atrasentan is an ET-A antagonist that is being studied extensively in metastatic prostate cancer. Initial Phase II trials showed decreased rates in PSA rise and delayed time to progression, as well as improvement in patient-reported outcomes [13,14]. A randomized placebo-controlled Phase III trial that accrued 809 CRPC patients was stopped early due to lack of efficacy [15]. A second large placebo-controlled trial, showed, during preliminary analysis that showed the patients on the atrasentan arm had less disease progression and longer time to progressions [16]. Currently, there

is a Phase III trial underway using atrasentan in combination with docetaxel being conducted by ECOG.

A second ET receptor inhibitor in clinical trial is ZD4054. The drug has had effective preclinical and clinical inhibition of the ET-A receptor. In addition, this drug may provide more selective inhibition of the receptor. A double-blind, randomized Phase II study of 312 chemo-naïve patients with CRPC and bone metastases randomized patients to receive oral once-daily ZD4054 15 mg (n = 98), 10 mg (n = 107) or placebo (n = 107). PFS was the primary end point, and OS was a secondary end point. There was no difference in PFS between the three arms. Patients who received ZD4054 10 mg once daily had a median OS of 24.5 months, patients who received ZD4054 15 mg once daily had a median OS of 23.5 months and the placebo arm had a median OS of 17.3 months [17]. A randomized, Phase III, placebo-controlled trial in chemotherapy-naïve men with asymptomatic metastatic CRPC with survival as the primary end point is being developed that will look at docetaxel with or without ZD4054.

Antisense therapeutics

In prostate cancer, several molecular changes lead to uncontrolled growth and, subsequently, tumor metastasis. These molecular targets are overexpressed, and can lead to therapeutic resistance, so provide an ideal target in the therapy of prostate cancer. Although there are several genes that are overexpressed, the ones that are selectively overexpressed are those that provide the most therapeutically beneficial target. In addition, since these genes can lead to resistance of chemotherapeutic agents, the potential to knockdown these genes and regain sensitivity is a possibility.

One enzyme target is ribonucleotide reductase, which helps in tumor growth and division. GTI-2040 is a first-generation phosphothioate antisense molecule that inhibits ribonucleotide reductase. A Phase I study of tumors refractory to chemotherapy demonstrated that the therapy was well tolerated. In addition, four out of 36 patients had disease stabilization: pancreatic (1), colorectal (2) and renal cell (1) cancers [18]. Preliminary results from a Phase II study that evaluated GTI-2040 in combination with docetaxel and prednisone in patients who had no prior chemotherapy demonstrated PSA declines of 50% in 9/22 patients. There was one partial response and nine patients had stable disease [19]. In this single-arm study, any added clinical benefit of GTI-2040 is difficult to quantify.

Clusterin is a stress-induced cytoprotective chaperone that inhibits treatment-induced cell death through several varied mechanisms. OGX-011 is able to downregulate the expression of the clusterin gene. A Phase I trial of OGX-011 in combination with docetaxel was conducted in refractory solid tumors. There were 26 patients (nine prostate, eight ovary, three NSCLC, four renal, one breast and other) enrolled with doses of OGX up to 640 mg delivered with weekly docetaxel. OGX-011 side effects were minimal to moderate. Serial baseline serum clusterin levels were monitored and found to decrease. Of 18 patients with measurable disease, there has been one partial response and five patients with stable disease. Several trials are now being conducted with OGX-011 in castrate-resistant prostate cancer in combination with docetaxel both in the first-line and second-line setting [20].

Other targeted agents

Sorafenib is a multitargeted tyrosine kinase inhibitor, which, in particular, inhibits vascular endothelial growth factor receptor-2, b-ras and c-Ras. Sorafenib has been evaluated in a Phase II trial in chemotherapy-naïve patients. Preliminary results of a Phase II trial are being conducted by our group here at the NIH Clinical Center using a two-stage design with 24 patients enrolled in Stage II in which 60% of patients had received one prior chemotherapy regimen. A total of 21 patients had evaluable disease. Eight patients had stable disease with a median duration of 16.5 weeks, even with rising PSAs. Toxicities likely related to treatment include: grade 3 hypertension and hand-foot syndrome, and grade 1/2 fatigue, anorexia, hypertension, skin rash, nausea and diarrhea. Eleven out of 21 patients had a dose reduction. In addition, more patients (6) than anticipated were unable to tolerate therapy and came off the study.

Sunitinib is a receptor tyrosine kinase inhibitor that inhibits several different targets (VEGF, KIT and FLT-3) that are implicated in prostate cancer progression and bone metastasis. A Phase I study of 19 patients with metastatic prostate cancer received sunitinib in combination with docetaxel and prednisone. Interestingly, there was a rise in PSA during the lead-in with sunitinib. The grade 3–4 adverse events were neutropenia (29%), fatigue (12%) and thrombocytopenia (6%). Of seven patients with measurable disease, there was partial response (in one) and stable disease in four. A confirmed PSA response (50% decrease in PSA) occurred in 5/15 patients [21].

FK 228 is a bicyclic depsipeptide that inhibits histone deacetylase. Early results from an ongoing Phase II trial of FK 228 in chemotherapy-naïve patients who had castrate metastatic prostate cancer show that of the 16 patients included in this interim report, 12 were evaluable for radiologic response. One patient achieved a confirmed radiographic partial response, and four others had stable PSA values on treatment. The most common adverse events were fatigue, nausea and vomiting [22].

Bortezomib is the first clinically studied reversible inhibitor of the 26S proteasome that is involved in the catabolic pathway for many intracellular proteins. A Phase I/II study was conducted with 83 patients, approximately half of whom were chemotherapy naïve. Significant PSA declines ($\geq 50\%$) occurred in 19 (28%) of 67 evaluable patients and was maintained for more than 4 weeks in 14 patients (21%). In patients with measurable disease, a partial response was seen in 11%, and an additional 67% had stable disease. Fatigue and diarrhea were the most common drug-related adverse event. No clinically significant febrile neutropenia or neuropathy occurred [23].

Conclusion

The limited therapy that is currently available for metastatic castrate-resistant prostate cancer has allowed for exploration of more molecular targets. These molecular targets have been implicated in

progression of disease but, also in resistance to different chemotherapeutic agents. Although docetaxel has shown moderate survival benefit in patients with metastatic prostate cancer, there are still other targets that have not been explored as single agents or in combination therapy. Initial trials have looked mainly at single-agent therapy with minimal efficacy, but several of these agents are being found to be beneficial as combination therapy with chemotherapeutic agents.

The current chemotherapeutic agents also have the disadvantage of having several side effects involved. The current trials illustrate that the targeted therapies are not only helping in progressive disease or resistance, but are extremely well-tolerated in individuals. The therapies, even when given daily, appear to be associated with minimal side effects. Even with combination therapy there appears to be very minimal toxicity. This is another reason that further exploration of these targets is warranted, both as single agents and in combination therapies. Although only a few of the targeted therapies that are available have been mentioned, there are still several targets that have not been explored. However, of the therapies that have been mentioned, it does appear that the class of anti-angiogenic therapies may provide the most substantial benefit for patients with CRPC. In addition, combinations of different anti-angiogenic therapies may provide even greater benefit than monotherapy as multiple targets may be affected.

Executive summary
Anti-angiogenesis therapy • Bevacizumab has been combined with several agents: – Docetaxel and estramustine – Docetaxel and prednisone – Thalidomide and lenalidomide has been combined with: – Docetaxel – Docetaxel, bevacizumab and prednisone – Cediranib a small-molecule VEGF inhibitor used monotherapy: – Combined with docetaxel and prednisone
Growth inhibitors • Calcitriol has shown some benefit in initial trials, but similar advantages have not been seen in larger trials. • Atrsentan, an edothelin-A inhibitor, is currently in Phase III combination trial with docetaxel.
Antisense therapeutics • GTI-2040, inhibitor of ribonucleotide reductase, has shown initial benefits in combination with docetaxel and prednisone. • OGX-011 downregulates clusterin. Ongoing studies with docetaxel in the first- and second-line setting are taking place.
Other targeted inhibitors • Sorafenib, a multitargeted tyrosine kinase inhibitor, as monotherapy has not been promising and combination trials are ongoing. • Sunitinib, a multitargeted tyrosine kinase inhibitor, as monotherapy has shown some initial benefit and combination studies are ongoing. • FK 228, a HDAC inhibitor, has some initial benefit in monotherapy trials. • Bortezomib, a proteasome inhibitor that has shown some initial positive results in early trials as monotherapy, has ongoing trials in combination with docetaxel and mitoxantrone.

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Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. US Cancer Statistics Working Group. United States Cancer Statistics: 2003 Incidence and Mortality. US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, Atlanta (2006)
2. Goktas S, Crawford ED: Optimal hormonal therapy for advanced prostatic carcinoma. *Semin. Oncol.* 26(2), 162–173 (1999).
3. Klotz L: Hormone therapy for patients with prostate carcinoma. *Cancer* 88(Suppl. 12), 3009–3014 (2000).
4. Petrylak DP, Tangen CM, Hussain MH *et al.*: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N. Engl. J. Med.* 351(15), 1513–1520 (2004).
- **Pivotal study demonstrating the overall survival benefit of docetaxel and prednisone every 3 weeks.**
5. Tannock IF, de Wit R, Berry WR *et al.*: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* 351(15), 1502–1512 (2004).
- **Pivotal study demonstrating overall survival advantage of docetaxel/prednisone versus mitoxantrone/prednisone.**
6. Picus J, Halabi S, Rini B *et al.*: The use of bevacizumab with docetaxel and estramustine in hormone refractory prostate cancer: Initial results of CALGB 90006. *ASCO Prostate Cancer Symposium 2007*, FL, USA (2003) (Abstract 1578).
7. Dahut WL, Gulley JL, Arlen PM *et al.*: Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J. Clin. Oncol.* 22(13), 2532–2539 (2004).
8. Moss RA MSG, Shelton G, Melia J, Petrylak DPA: Phase I open-label study using lenalidomide and docetaxel in androgen independent prostate cancer (AIPC). *ASCO Prostate Cancer Symposium 2007*, FL, USA (2007) (Abstract 89).
9. Ryan CJ, Stadler WM, Roth B *et al.*: Phase I dose escalation and pharmacokinetic study of AZD2171, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase, in patients with hormone refractory prostate cancer (HRPC). *Invest. New Drugs* 25(5), 445–451 (2007).
10. Beer TM, Eilers KM, Garzotto M, Egorin MJ, Lowe BA, Henner WD: Weekly high-dose calcitriol and docetaxel in metastatic androgen-independent prostate cancer. *J. Clin. Oncol.* 21(1), 123–128 (2003).
11. Beer TM, Ryan CW, Venner PM *et al.*: Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. *J. Clin. Oncol.* 25(6), 669–674 (2007).
12. Novacea Halts ASCENT-2 Trial in Advanced Prostate Cancer. *RxTrials Institute Drug Pipeline Alert* 5(218) (2007).
13. Carducci MA, Padley RJ, Breul J *et al.*: Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, Phase II, placebo-controlled trial. *J. Clin. Oncol.* 21(4), 679–689 (2003).
14. Nelson JB, Nabulsi AA, Vogelzang NJ *et al.*: Suppression of prostate cancer induced bone remodeling by the endothelin receptor A antagonist atrasentan. *J. Urol.* 169(3), 1143–1149 (2003).
15. Lipton A, Sleep D, Hulting S, Isaacson D, Allen A: Benefit of atrasentan in men with hormone refractory prostate cancer. 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition) 22(14S), 4687 (2004)
16. Nelson JB, Chin J, Love W *et al.*: Results of a Phase 3 randomized controlled trial of the safety and efficacy of atrasentan in men with nonmetastatic hormone-refractory prostate cancer (HRPC). *ASCO Prostate Cancer Symposium 2007*, FL, USA (2007) (Abstract 146).
17. James ND BM, Zonnenberg B *et al.*: ZD4054, a potent, specific endothelin A receptor antagonist, improves overall survival in pain-free or mildly symptomatic patients with hormone-resistant prostate cancer (HRPC) and bone metastases. In: *14th European Cancer Conference (ECCO)* (2007).
18. Desai AA, Schilsky RL, Young A *et al.*: A Phase I study of antisense oligonucleotide GTI-2040 given by continuous intravenous infusion in patients with advanced solid tumors. *Ann. Oncol.* 16(6), 958–965 (2005).
19. Sridhar S, Canil C, Hotte S *et al.*: A Phase II study of the antisense oligonucleotide GTI-2040 plus docetaxel and prednisone as first line treatment in hormone refractory prostate cancer (HRPC). *2006 ASCO Annual Meeting*, GA, USA (2006) (Abstract 13015).
20. Ongoing Trials: OncoGenex Technologies Inc. (2007).
21. Zurita A, Shore N, Kozloff M *et al.*: Phase I study of sunitinib in combination with docetaxel and prednisone in patients (pts) with metastatic hormone refractory prostate cancer (mHRPC). *ASCO Prostate Cancer Symposium 2007*, FL, USA (2007) (Abstract 230).
22. Molife R, Patterson S, Riggs C *et al.*: Phase II study of FK228 in patients with metastatic hormone refractory prostate cancer (HRPC). *ASCO Prostate Cancer Symposium 2007*, FL, USA (2006). (Abstract 207).
23. Dreicer R, Petrylak D, Agus D, Webb I, Roth B: Phase I/II study of bortezomib plus docetaxel in patients with advanced androgen-independent prostate cancer. *Clin. Cancer. Res.* 13(4), 1208–1215 (2007).