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Seminar article

New drug development in metastatic prostate cancer

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Abstract

In 2007, drug development in castration-resistant metastatic prostate cancer (CRPC) remains challenging, due to the number of potentially viable molecular targets and clinical trials available, the lack of established surrogates for overall survival, and competing causes of mortality. This review will highlight the highest impact phase II and phase III trials of novel agents in the current CRPC landscape, and focus on both molecular targets and clinical trial designs that are more likely to demonstrate clinical benefit. The need for tissue correlative studies for target evaluation and drug mechanism is stressed to continue to advance the field and to define biomarkers that may identify patient populations that may derive a greater benefit from these molecular agents.

Keywords: Drug development; Prostate cancer; Hormone refractory; Novel agents; Chemotherapy; Angiogenesis; mTOR; Immunotherapy; Vitamin D; HDAC inhibitors; Castration-resistant

Introduction

Prostate cancer in 2007 remains the second most common cause of cancer death [1]. Docetaxel and prednisone (DP) were approved by the United States Food and Drug Administration (USFDA) in 2004 for the palliative management of men with castration-resistant prostate cancer (CRPC), based on improved survival, tumor response, pain and quality-of-life responses, and tolerability [2]. As such, the 3-weekly schedule of DP has replaced mitoxantrone and prednisone (MP) as the standard of care in men with metastatic CRPC, and has become the backbone of current drug development in CRPC, either as a comparator arm or the foundation on which to add novel agents [3]. For example, Cancer and Leukemia Group B (CALGB) 90401 is currently enrolling patients in a phase III trial of DP vs. DP with bevacizumab to evaluate the survival benefits of anti-angiogenic therapy in CRPC. The remainder of this review will discuss the development of these targeted agents and trial designs for men with CRPC, summarized in Table 1, as an active list of select agents that are in phases II and III clinical trials for this disease. Previously approved agents, such as docetaxel, mitoxantrone, hormonal (including novel anti-androgens) agents, and bisphosphonates are addressed elsewhere in this seminar.

Perspectives on drug development in CRCP

As molecularly targeted agents enter clinical trials in CRPC, one dilemma is how to ascertain response or clinical benefit to these agents. While 3-month PSA declines are generally expected in the evaluation of cytotoxic agents, PSA response criteria have not been developed for molecularly targeted cytostatic or anti-angiogenic agents [4,5]. As PSA simply represents a biomarker and a potential intermediary between treatment exposure and survival as an outcome, a surrogacy evaluation of this biomarker should be considered before using it as a primary endpoint in trials of novel agents [4,5]. Molecularly targeted agents may act independently of the androgen receptor that drives PSA production, and may even temporarily increase PSA as tumor volume declines due to differentiating effects, or provide clinical benefit without major alterations in PSA dynamics [6,7]. In addition, definitions of progression remain problematic in CRPC, such that skeletal events, pain, visceral tumor measurements, and quality-of-life may all be potentially valid measures of clinical benefit [8,9]. A rigorous definition of progression-free survival that captures the

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Table 1
Select ongoing clinical trials of molecularly targeted agents in development for treatment of CRPC

Target	Agent	Phase	Overview of trial
Angiogenesis			
VEGF	Bevacizumab (Avastin®)	III	CALGB 90401: DP ± bevacizumab, first line metastatic CRPC
VEGF receptor	Sorafenib (Nexavar®)	II	CRPC single agent (NCI)
	Sunitinib (Sutent®)	II	First-line CRPC: DP + sunitinib (Pfizer)
	Vatalinib	II	DP + vatalinib, first line (Novartis)
PTEN/PI3 kinase mTOR pathway	Everolimus (RAD 001)	I/II	DP+ RAD001 first line metastatic CRPC (Novartis, Dana Farber/ DOD)
		II	Non-metastatic CRPC (Novartis, Duke)
	AP23573	II	Metastatic taxane-resistant CRPC (Ariad)
EGFR/HER2	Lapatinib (Tykerb®)	II	Rising PSA only (ECOG) or asymptomatic CRPC (GSK, UNC, and Duke)
Bone interface	Atrasentan (Xinlay)	III	SWOG 0421: First-line metastatic CRPC DP ± Atrasentan, first line (Abbott)
ET-A receptor	ZD4054		Phase III in CRPC (AstraZeneca)
RANK ligand	Denosumab (AMG 162)	III	Denosumab vs. zoledronic acid for palliation in CRPC (Amgen)
Immunotherapy	Provenge® (Sipuleucel-T)	III	D9902B: Provenge vs. placebo in asymptomatic CRPC (Dendreon)
	Prostate GVAX®	III	VITAL 1: DP vs. GVAX in asymptomatic CRPC (Cell Genesys)
			VITAL 2: DP vs. D + GVAX in symptomatic CRPC (Cell Genesys)
	Anti-CTLA4 antibody (MDX-010)	I/II	CRPC (DOD) first line (Medarex)
Nuclear targets			
Vitamin D	DN-101	III	ASCENT II: DP ± DN-101 (calcitriol) first line metastatic CRPC (Novacea, DOD)
Histone deacetylase (HDAC)	SAHA (Vorinostat, Zolinza®)	II	Second line CRPC (Michigan, DOD)
	LBH 589B	II	First line CRPC (Novartis)
Androgen receptor	Abiraterone acetate	III	Second line with prednisone vs. prednisone alone after docetaxel failure (Cougar Biotechnology)
	MDV-3100	I/II	CRPC (Medivation)

DOD = Department of Defense Prostate Cancer Consortium; CRPC = castration-resistant prostate cancer; DP = docetaxel and prednisone.

full effects of overall survival would be a significant advance in clinical trial development for men with CRPC. It is possible that a composite of tumor measures and pain measures may provide both a quantitative and qualitative measures of clinical benefit in symptomatic patients [8,10].

In 2007, overall survival remains the necessary primary endpoint in phase III clinical trials in men with CRPC, given the uncertain validity of other surrogate measures for clinical benefit [4,5,8]. However, phase II studies do require shorter term endpoints to assess clinical activity without the cost of a trial powered to detect an overall survival advantage. As tumor response by RECIST (Response Evaluation Criteria in Solid Tumors) criteria may not capture the full clinical benefits of cytostatic, anti-angiogenic, cancer stem cell, and immunomodulatory agents, trial designs that capture clinical benefit using other endpoints are likely to be necessary [11]. These endpoints may include progression-free survival, time to new metastasis, or composites of pain, tumor, and/or PSA progression. One such design is the randomized discontinuation trial (RDT). In the RDT, all patients are initially treated with the active agent, and randomization only occurs in those patients with stable disease after a period of observation [12]. Responding patients continue the agent, while primary progressing patients are removed quickly from the study. In this trial design, randomized patients are followed to a prespecified progression endpoint. One caveat to this design is the large number of patients who must be initially enrolled, especially if the stable or responding proportion is low, and the concerns over small numbers of patients whho actually make it to randomization [13]. This design, however, was relatively successful in the evaluation of sorafenib in renal cell carcinoma, and may encourage others to evaluate this design in prostate cancer.

Finally, trial designs that enrich for a molecular target or predictive biomarker may also lead to the more efficient identification of active molecular agents [14]. As in the case of the target Her2 and the agent trastuzumab in metastatic breast cancer, using a targeted agent in an unselected population may dilute the effects of that agent, and an otherwise active drug for a select population of cancer patients may go unnoticed. As genomic signatures and molecular targets are identified in prostate cancer, designs that take advantage of these markers will advance the field [15].

The collection of tumor or surrogate tissue for biomarker analysis, validation of molecular targets, prospective identification of drug mechanisms, and biologic basis for disease progression is highly encouraged and feasible in men with CRPC. While obtaining adequate tissue from bone biopsies can be challenging due to logistics, crush artifact, sample yield, and quality control, it is essential for moving the field forward by understanding resistance to our current therapies and identifying subgroups of patients who may benefit from these agents.

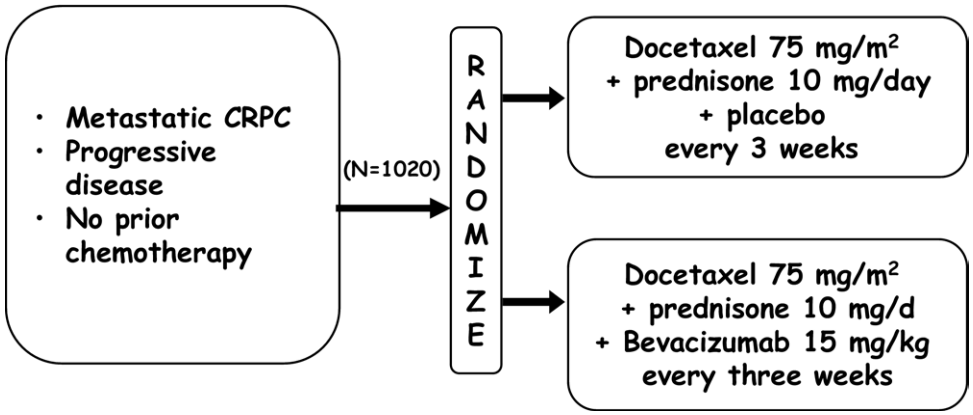

Fig. 1. Schema for CALGB 90401. Correlative science to evaluate and validate Halabi nomogram risk groups, PSA kinetics, plasma angiokine and cytokine levels, and PSA RT-PCR.

Molecular targets

Angiogenesis

As with many solid tumors, angiogenesis has an important position in prostate cancer progression. Microvessel density in clinically localized prostate cancer is an independent prognostic for progression and survival [16,17]. Moreover, through the CALGB, we demonstrated that the plasma level of vascular endothelial growth factor (VEGF), a potent angiogenic growth factor, is an independent prognostic factor in men with metastatic CRPC [18]. Anti-angiogenic agents utilizing monoclonal antibodies to VEGF, such as bevacizumab (Avastin®; Genentech, San Francisco, CA) have been studied in prostate cancer. While single agent studies have failed to demonstrate significant results, a phase II trial conducted by the CALGB added bevacizumab to docetaxel and estramustine in men with CRPC with 79% of patients having a greater than 50% PSA, median time-to-progression of 9.7 months, and overall median survival of 21 months [19]. Based upon these promising results, a randomized, double-blind placebo-controlled phase III trial has been designed comparing docetaxel 75 mg/m^2 every 3 weeks with prednisone 10 mg orally daily with either bevacizumab 15 mg/kg IV or placebo every 3 weeks (CALGB 90401), shown in Fig. 1. The primary endpoint for this trial is overall survival, and accrual of 1,020 patients is now complete.

Thalidomide and its analogs may inhibit angiogenesis and prostate tumor growth through multiple potential mechanisms, including inhibition of pro-angiogenic signals such as VEGF as well as immunomodulatory effects by affecting T-cell co-stimulatory activity [20]. A recent randomized Phase II study of thalidomide in combination with docetaxel in hormone-refractory disease demonstrated an impressive 53% PSA decline (>50% decrease in PSA), and improved TTP and OS [21]. The study was underpowered and toxicities of this combination therapy included high rate of thrombosis, sedation, and neuropathy. Interest in the continued development of more potent thalidomide analogs, such as lenalidomide (Revlimid®; Celgene, Summit, NJ), has led to its development in a Phase II trial through the Department of Defense Prostate Cancer Consortium in men with a rising PSA after local therapy.

Evaluation of tyrosine kinase inhibitors (TKI), which inhibit angiogenic growth factor receptors signaling in advanced prostate cancer, has recently begun. In addition to VEGF, another potential angiogenic growth factor target inhibited by several TKI is platelet derived growth factor (PDGFR). Prostate cancer cells have been shown to express high levels of platelet-derived growth factor receptor (PDGFR), which in turn enhances the PI3 kinase/Akt pathway leading to prostate cancer progression [22]. Sorafenib (Nexavar®; Bayer Pharmaceuticals, West Chester, PA) is an oral agent that inhibits RAF kinase, VEGF receptor tyrosine kinase, and the PDGF receptor, and is currently approved for metastatic renal cell carcinoma based on improved progression-free survival [23,24]. A Phase II study of 22 patients evaluated the activity of sorafenib in CRPC [25]. Of the 19 patients who progressed, 10 progressed with PSA rise only and 2 patients with PSA progression where found to have dramatic resolution of bony disease. Vatalinib (PTK787/ZK 222584; Novartis Pharmaceuticals, East Hanover, PA) is another multi-targeted TKI inhibiting VEGFR 1–3 and PDGFR at nanomolar concentrations [26]. We performed a small Phase I study to evaluate preliminary efficacy in metastatic CRPC patients. Overall, 1 out 19 patients demonstrated >50% reduction from baseline in serum PSA level and duration of response of 12 months; 2 other patients demonstrated >40% reductions in PSA with duration of 4 and 5 months, respectively [27]. These results have raised the question of the validity of PSA response and progression measures for the evaluation of this class of agents, and further study using clinical endpoints seems warranted.

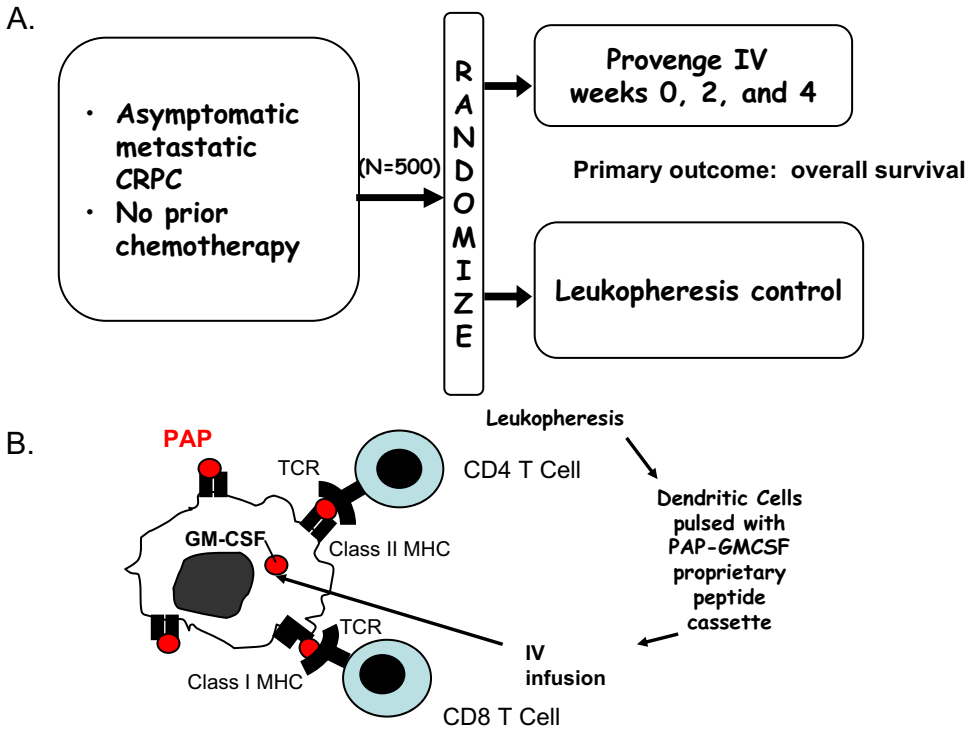

Fig. 2. Schema (A) and diagram (B) of the IMPACT study investigating autologous dendritic cell vaccination in men with CRPC. (Color version of figure is available online.)

Cell survival and growth pathways

The growth and survival addiction to mutated oncogenic signaling pathways may be both the source of cancer progression and a potential weakness for therapeutic exploitation [28]. Strategies that target these molecular lesions in prostate cancer are rational and dynamic as the mechanisms of prostate cancer progression and resistance to current therapies are dissected. One such molecular lesion is the tumor suppressor phosphatase and tensin homolog deleted on the chromosome 10 (PTEN), whose expression is lost in the majority of advanced prostate cancer cases [29,30]. Loss of PTEN leads to unrestrained phosphatidylinositide 3-kinase (PI3K)/Akt activity and cellular survival signaling. One downstream target of this pathway is mTOR kinase mammalian target of rapamycin (mTOR), which regulates cell size, translation of key growth, survival, and angiogenic signals [31,32]. Multiple mTOR inhibitors exist, including temsirolimus (CCI-779; Wyeth, Collegeville, PA), everolimus (Novartis, Cambridge, MA), AP23573 (Ariad, Cambridge, MA), and rapamycin itself. Phase I and preprostatectomy studies of these agents have demonstrated early signs of successful target inhibition in prostate cancer and are ongoing [33,34]. RAD001 is also being evaluated in combination with docetaxel and prednisone in men with CRPC, given the potential for mTOR inhibitors as chemosensitizing agents [35].

Another potential target involved in cellular growth includes the HER2/neu (ErbB-2) tyrosine kinase. HER-2 expression has been shown to increase androgen receptor activation leading to growth of prostate cells [36]. Phase II studies of the EGFR TKI gefitinib (Iressa®; AstraZeneca, Waltham, MA) and the anti-Her2 monoclonal antibody trastuzumab (Herceptin®; Genentech, San Franciso, CA) showed low levels of efficacy in CRPC, possibly due to the low prevalence of HER2 over-expression [37,38]. Phase II studies are ongoing in men with PSA relapse and CRPC using the dual EGFR/HER-2 kinase inhibitor, Lapatinib (Tykerb®; GlaxoSmithKline, Philadelphia, PA) [39]. Understanding resistance to EGFR/HER2 directed therapies may lead to the identification of additional targets [40].

Immunotherapy

Entraining the immune system to overcome tumor-induced tolerance is the goal of nearly every cancer vaccine program. In prostate cancer, strategies to target the immune system have included autologous (self) and allogeneic (non-self) vaccines, protein-based and whole cell vaccines, and blockade of immunosuppressive signals [41]. Induction of the immune system against normal and cancerous prostate tissue has been demonstrated by vaccination with prostate specific proteins/peptides including PSA (prostate-specific antigen), prostatic acid phosphatase (PAP), and prostate specific membrane antigen (PSMA) [42]. Two types of immunotherapies that are in phase III trials include autologous dendritic cell-based immunotherapy and allogenic whole cell based immunotherapy (Figs. 2 and 3). Most of

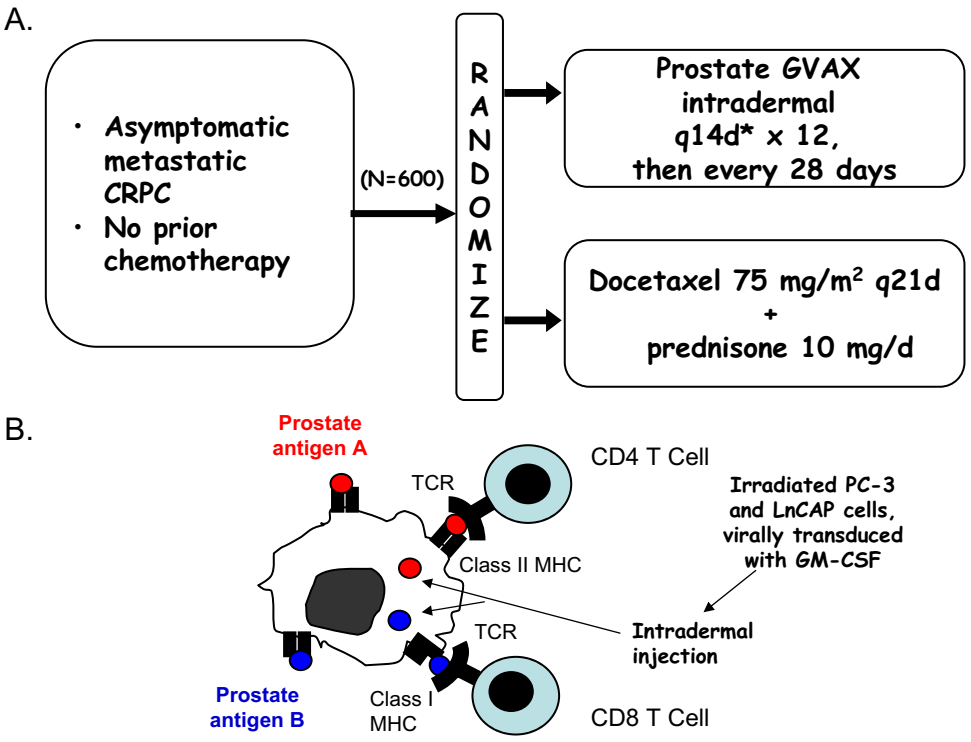

Fig. 3. Schema (A) and diagram (B) of the VITAL-1 study investigating off-the shelf whole cell allogeneic prostate cancer vaccination in men with CRPC. (Color version of figure is available online.)

the current vaccine-based therapeutic approaches use granulocyte-macrophage colony stimulating factor (GM-CSF), a cytokine that improves antigen presentation and activation of T-cells.

Provenge (Sipuleucel-T; Dendreon, Seattle, WA) is an example of dendritic cell-based therapy. Leukopheresed dendritic cells are collected from patients and then are pulsed with a proprietary fusion product of GM-CSF and PAP. A phase II-III placebo-controlled trial studied 127 patients with asymptomatic CRPC and found a trend to increased time to progression (1.7 week difference, $P = 0.052$). A statistically significant improvement in overall survival in the vaccine treated group was noted as a secondary endpoint (25.9 vs. 21.4 months, $P = 0.01$) [43]. Vaccine was well tolerated, with the most common side effects including infusion reactions such as rigors and pyrexia. Although the trial was not powered to show survival benefit, the initial results show promise, and a confirmatory phase III trial (IMPACT, D9902B) is ongoing in men with minimally symptomatic CRPC (Fig. 2).

Prostate GVAX® (Cell Genesys, San Francisco, CA) is immunotherapy using inactivated allogenic prostate carcinoma cell lines (PC-3 and LnCaP), which are modified genetically through adenoviral transfer to secrete GM-CSF [44]. The advantage is that the vaccine can be manufactured in large quantities and multiple tumor antigens can be targeted. A disadvantage is the relative weakness of individual antigens in this approach, requiring repeat dosing. Two phase II trials have demonstrated activity with one trial showing an overall survival of 26 months and another trial showed improvement of osteoclast activity in a majority of patients and expected overall survival data to be greater than 24.4 months [45]. As these were uncontrolled trials in an asymptomatic population with an expected survival to be relatively high, it remains unclear as to the true benefit of this approach. The vaccines were well tolerated, with common side effects including injection site reactions, fatigue, malaise, myalgias, and arthralgias, without any dose-limiting toxicities. Two phase III trials that are currently ongoing will further test the response to vaccines vs. standard chemotherapy. VITAL-1 has accrued 600 men with asymptomatic in hormone-refractory prostate cancer with no prior chemotherapy, and randomized these men to GVAX vs. docetaxel/prednisone, with the primary end point being overall survival (Fig. 3). VITAL–2 plans to accrue 600 men with symptomatic CRPC and randomize to docetaxel with or without GVAX.

Nuclear receptors targets

Multiple epidemiological studies have shown an increased risk of prostate cancer with relative vitamin D deficiency [46]. Vitamin D receptors are expressed in prostate cancer cells; prostate cancer cells are deficient in converting 25-hydroxyvitamin D to 1,25-hydroxyvitamin D, an active differentiating agent in prostate cancer [47]. In vitro studies have shown that calcitriol (1,25-dihydroxycholecalciferol) may be able to inhibit growth and promote differentiation of prostate

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