Novel approaches and future directions in castration-resistant prostate cancer

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Recent advances in the treatment of castration-resistant prostate cancer (CRPC) have started to change the therapeutic landscape allowing clinicians to choose from a broad range of treatment options. Understanding the mechanisms that transform prostate cancer (PCA) into a castration-resistant state has enabled investigators to explore critical pathways involved in such process allowing for rational therapeutic design. These novel therapies complement the modest success that chemotherapy has demonstrated in recent years.

In this review, we discuss the different mechanisms that render PCA castration resistant and elaborate on the nonchemotherapy approaches evolving in CRPC. These include agents targeting the epidermal growth factor receptor, endothelin receptor antagonists, angiogenesis inhibitors, immunomodulatory agents, immunotherapy, novel antiandrogens, and delivery of cytotoxic agents via therapeutic antibodies. This timely review coincides with the identification of newer therapies in this setting affirming our steady movement towards better disease control.

Key words: angiogenesis, castration resistant, immunotherapy, immunomodulatory agents, prostate cancer, receptor antagonists

Introduction

Prostate cancer (PCA) is the most diagnosed cancer and the third leading cause of cancer deaths in USA men with an estimated 198,280 diagnosed cases in 2009 translating into 27,360 deaths annually [1]. Despite early screening, many patients are diagnosed at advanced stage [2].

The initial approach to advanced PCA is medical or surgical androgen deprivation therapy (ADT) or antiandrogens [3]. However, all advanced PCAs become refractory to hormonal therapies [4]. When progression occurs despite ADT, the disease is considered castration resistant with a traditional median survival of 18 months in metastatic patients using docetaxel-based therapies [5–7].

In this review, we discuss mechanisms of castration resistance and putative therapeutic modalities. We then expand on noncytotoxic approaches, specifically novel antiandrogens, angiogenesis inhibitors, immunomodulatory agents, immunotherapy, and therapeutic antibodies. This review is timely as a number of novel agents have become available for treatment and investigation.

Proposed mechanisms of castration resistance

Multiple mechanisms for emergence of the castration-resistant state have been proposed, including androgen receptor (AR) overexpression, alteration in AR structure or function, intratumoral androgenic steroid synthesis, ligand-independent AR activation by growth factor pathways, as well as AR-independent mechanisms (Figure 1) [8].

The AR is the primary driving force for PCA cell replication and survival. As demonstrated by Chen et al. [9], AR gene and protein up-regulation during tumor progression is the most common and mechanistically critical event in the development of castration-resistant prostate cancer (CRPC). Furthermore, overexpression of AR leads to activation despite lower levels of circulating androgens [10]. In addition, mutations in AR that decrease receptor specificity and allow its activation by nonandrogen ligands, endogenous steroids, and even antiandrogens have been described [11]. Finally, overexpression of enzymes involved in androgenic steroid synthesis may lead to the observed increased intratumoral androgens in CRPC [12].

Neuroendocrine differentiation, which prevails in >40% of CRPC, induces an alternate route for development of castration resistance [11]. Evidence suggests that neuroendocrine cells represent terminally differentiated and androgen-insensitive populations [13]. Furthermore, neuroendocrine peptides alter the microenvironment promoting castration-resistant cell growth [14]. In addition, the absence of proliferative and apoptotic activity in neuroendocrine tumor cells explains their resistance to cytotoxic and radiation therapies contributing to continued disease progression [15].

Genetic deregulation is another important pathway in CRPC development and progression. The PTEN tumor suppressor
gene is commonly mutated in CRPC eliminating the inhibitory effect on the phosphatidylinositol 3-kinase (PI3-K) pathway, causing overproduction of AKT and the ensuing cell survival [11, 16]. Whether PTEN mutations contribute to the evolution of PCA or the development of castration resistance remains debatable [17]. In early stages, patients who have PTEN mutation demonstrate higher Gleason score and worse prognosis with increased risk for metastasis [18]. In later stages, the onset of hormone independence can result from activation of the AKT pathway [19]. Accordingly, PTEN mutations play an integral role in disease recurrence at early stages and in CRPC progression. In addition, deregulation of proapoptotic oncogenes, such as bcl-2, a primary target of AKT, allows for cell survival and disease progression [20, 21].

Additional theories for CRPC development include the loss of immune regulation and enhanced tumor angiogenesis [22, 23]. Several pathways are likely involved in disease progression making targeting one pathway an insufficient approach and arguing that combinations could offer better disease control [24]. Understanding these mechanisms has allowed the development of newer strategies in CRPC challenging the modest results offered by standard systemic chemotherapy (Table 1). However, despite their theoretical rationale, these pathways do not always prove to be therapeutically effective underscoring the limitations of our perception of this disease (Table 2).

**novel antiandrogens and androgen synthesis inhibitors**

The evidence that AR up-regulation leads to increased sensitivity to circulating and intratumoral androgentic steroids suggests that more complete blockage of AR–ligand interaction may have efficacy in CRPC. Abiraterone acetate specifically inhibits the 17 alpha-hydroxylase and C17,20-lyase (CYP450c17) enzymes within the adrenal synthetic pathway, with subsequent decrease in testosterone production in castrate and non-castrate PCA [28, 29]. Several studies have evaluated this agent in chemotherapy-naive patients and in docetaxel failures [30, 31]. Response rates ranged from 45% in heavily pretreated individuals to 75% in chemotherapy-naive patients. Phase III trials comparing abiraterone with prednisone in docetaxel failures have been completed and are soon to be reported [32]. An alternative CYP17 inhibitor, TAK700 is also under investigation and has demonstrated antitumor effects [33]. MDV-3100 is an AR inhibitor with greater binding affinity to the receptor than bicalutamide in CRPC cells overexpressing the AR [34]. Phase I and II studies confirmed biochemical responses in chemotherapy-failure patients and in those who were chemotherapy naive [35]. These studies have challenged the concept of ‘hormone sensitivity’ and have clearly demonstrated that the AR pathway remains critical to support growth and progression of PCA, even in the castrate state. The role of these agents vis-à-vis traditional cytotoxic therapy and
growth factors and their receptors

The overexpression of epidermal growth factor receptors (EGFRs) in >40% of CRPC cells paved the way to exploring EGFR inhibitors in this disease [36]. The overexpression of the HER-2 oncoprotein in CRPC led to studying trastuzumab in a small phase II trial where only 2 patients of 18 showed stable disease (SD) and reduction in serum prostate-specific antigen (PSA) [37]. However, detection of the HER-2 oncoprotein in CRPC varies with disease state arguing that better patient selection or combining trastuzumab with chemotherapy might be a better approach [38].

Based on in vitro studies [39], gefitinib was studied in CRPC, but clinical efficacy was not demonstrated [40, 41]. Alternatively, when combined with chemotherapy, gefitinib was safe, well tolerated, with a suggestion of efficacy [42].

Festuccia et al. [43] suggested that erlotinib might be active in chemotherapy-naive PCA cell lines. Accordingly, a phase II study evaluated the activity of single-agent erlotinib in previously untreated CRPC patients [44]. Patients who received erlotinib demonstrated biochemical responses with manageable and expected toxic effects. The 1- and 2-year survival rates were 58% and 27%, respectively [44]. In addition, combining erlotinib with docetaxel proved safe but the added benefit of this combination remains questionable [45]. Collectively, these studies suggest that EGFR inhibitors have minimal activity in CRPC. Unless additional data emerge, it remains unclear if the EGFR is a viable therapeutic target in CRPC.

Preclinical studies showed high levels of platelet-derived growth factor in primary and metastatic PCA [46, 47]. Imatinib is a platelet-derived growth factor receptor (PDGFR) inhibitor that has shown minimal activity as a single agent, which could be explained by its ability to lower tumor interstitial hypertension without direct antitumor activity [48–50]. Targeting the microenvironment justifies combining PDGFR inhibitors with cytotoxic therapy since antistromal activity enhances tumor uptake of cytotoxic agents [51, 52]. However, this modest increase in efficacy must be balanced against an increase in side-effects as seen in a study where imatinib combined with docetaxel and estramustine demonstrated higher incidence of thromboembolic events [53]. Agents targeting the PDGFR pathway seem to have minimal activity but their use in combination therapies remains under investigation.

Table 1. Pivotal chemotherapy regimens in CRPC

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>OS (months)</th>
<th>RR</th>
<th>PFS (months)</th>
<th>Common toxic effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + prednisone [5]</td>
<td>19.2</td>
<td>45% PSA, 12% visceral, 35% pain</td>
<td>NR</td>
<td>Neutropenia, GI toxicity, neuropathy</td>
<td>Standard first line</td>
</tr>
<tr>
<td>Mitoxantrone + prednisone [5]</td>
<td>16.3</td>
<td>32% PSA, 7% visceral, 22% pain</td>
<td>NR</td>
<td>Neutropenia</td>
<td>First-line setting</td>
</tr>
<tr>
<td>Satraplatin + prednisone [26]</td>
<td>15.3</td>
<td>25% PSA, 8% visceral, 24% pain</td>
<td>3.4</td>
<td>N/A</td>
<td>Second line after docetaxel failure</td>
</tr>
<tr>
<td>Cabazitaxel + prednisone [5]</td>
<td>15.1</td>
<td>39% PSA, 14% visceral, 9% pain</td>
<td>2.8</td>
<td>Neutropenia and febrile neutropenia</td>
<td>Second-line phase III study compared with prednisone and docetaxel failures</td>
</tr>
</tbody>
</table>

Table 2. Potential targeted options in CRPC

<table>
<thead>
<tr>
<th>Target</th>
<th>Function</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Membrane-bound receptor that promotes cell replication, overexpressed in prostate cancer cells</td>
<td>Gefitinib, erlotinib</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Signaling protein that stimulates cell growth and angiogenesis</td>
<td>Imatinib mesylate</td>
</tr>
<tr>
<td>Endothelin receptor</td>
<td>Membrane-bound receptor that functions in signal transduction promoting cell growth, differentiation, and angiogenesis</td>
<td>Atrasentan</td>
</tr>
<tr>
<td>mTOR</td>
<td>Protein kinase-regulating growth factor and nutrient/energy signaling through the Akt/P3 kinase pathway</td>
<td>Temsirolimus and everolimus</td>
</tr>
<tr>
<td>VEGF</td>
<td>Potent regulator of angiogenesis</td>
<td>Bevacizumab, thalidomide, lenalidomide</td>
</tr>
<tr>
<td>Raf kinase</td>
<td>Protein involved in signal transduction</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>PSMA</td>
<td>A membrane-bound glycoprotein produced by prostatic epithelium that is up-regulated after ADT</td>
<td>MAbs and radioimmunoconjugates</td>
</tr>
</tbody>
</table>

CRPC, castration-resistant prostate cancer; OS, overall survival; RR, response rate (classified as PSA response, visceral response using RECIST criteria, or pain relief response); PFS, progression-free survival; PSA, prostate-specific antigen; NR, not reported; GI, gastrointestinal; N/A, not available.
Dasatinib, an oral SRC and SRC family kinase inhibitor with direct antistromal properties, has shown in vitro activity against PCA [54]. Forty-seven chemotherapy-naive CRPC patients were enrolled in a phase II study receiving dasatinib (initial dose 100 mg twice daily, n = 25; 70 mg twice daily, n = 22), of whom 41 (87%) had bone disease. Lack of progression was achieved in 20 (43%) patients at week 12 and in 9 (19%) patients at week 24. Responding patients demonstrated a reduction in bone disease [55]. This activity led to a phase III trial comparing docetaxel plus dasatinib with docetaxel alone [56].

**endothelin receptor inhibitors**

Endothelins are important regulators of angiogenesis and signal transduction [57]. Their function is mediated through the ET<sub>A</sub> and ET<sub>B</sub> receptors. Generally, binding to ET<sub>A</sub> induces a survival pathway, whereas binding to ET<sub>B</sub> promotes apoptosis [58]. In CRPC, hypermethylation of the ET<sub>B</sub> promoter eliminates the negative growth response activating the ET<sub>A</sub> pathway exclusively [59]. Atrasentan is an ET<sub>A</sub> antagonist that prolonged time to PSA progression when compared with placebo in a phase II study conducted in asymptomatic men with CRPC [60]. Based on these results, a phase III randomized study in 941 men with nonmetastatic CRPC compared atrasentan 10 mg daily with placebo [61]. On an intent-to-treat analysis, median time to progression was 764 and 671 days with atrasentan and placebo (P = 0.2), respectively, without overall survival (OS) advantage. However, these negative results could be explained by the fact that 29% of patients discontinued therapy before reaching a protocol-defined end point [61]. Another phase III study in metastatic patients failed to show significant difference in time to disease progression although biologic activity was demonstrated [62].

While these results appear negative, the biologic activity of atrasentan [63] and the importance of the endothelin signaling axis in tumor growth in the bone [64] argue in favor of further studies. Identifying patients that might benefit from endothelin inhibitors or studying these agents at different disease stages might be important to demonstrate activity. Furthermore, combining atrasentan with docetaxel proved safe and effective with promising results [65]. Accordingly, the South West Oncology Group is conducting a randomized phase III trial comparing docetaxel and prednisone with and without atrasentan [66].

ZD4054 (zibotentan) is another specific ET<sub>A</sub> receptor antagonist with reported activity in CRPC [67]. A randomized phase II study of 312 metastatic CRPC patients demonstrated improvement in survival with ZD4054 compared with placebo without improvement in time to progression [68]. Accordingly, this agent is also being studied in combination with chemotherapy and at different disease stages.

**angiogenesis inhibitors**

Elevated levels of the vascular endothelial growth factor (VEGF) have been shown to correlate with advanced stage, progression, and poor survival in PCA [23, 69].

Bevacizumab is a humanized mAb that targets VEGF with demonstrated activity in several metastatic malignancies. A phase II study demonstrated synergy when bevacizumab and docetaxel were combined with >30% of patients showing radiographic responses [70]. Despite these promising results, bevacizumab did not improve the outcome in CRPC as the combination of docetaxel and bevacizumab, when studied in randomized phase III trial, failed to extend OS in this setting [71]. Importantly, more serious events and treatment-related deaths were observed with bevacizumab–docetaxel [71].

VEGF pathway inhibition can also be achieved by using a decoy fusion protein of different domains of the VEGF receptors [72]. Aflibercept is an angiogenesis inhibitor comprising portions of the extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G [73]. This agent has shown promising activity in refractory solid tumors [73, 74]. Combining aflibercept with docetaxel proved safe justifying further evaluation of this combination in CRPC [75].

Sorafenib is a novel oral small molecule that inhibits c-Raf-1 and B-raf, both essential proteins in signal transduction with well-documented antiangiogenesis properties [76]. Steinbild et al. [77] reported on a phase II study in chemotherapy-naive CRPC patients documenting PSA responses in 4.5% of assessable patients with >30% showing SD. A suggestion that sorafenib can overcome chemotherapy resistance in some patients who fail chemotherapy was recently reported [78]. In that study, patients who progressed on chemotherapy were allowed to continue chemotherapy with the addition of sorafenib. Biochemical responses were witnessed and the major toxicity was myelosuppression and skin toxicity [78]. Of importance, however, is the suggestion that PSA measurements might not be an adequate correlate for disease response in patients treated with sorafenib. Dahut et al. [79] showed that some patients with CRPC demonstrate radiographic response on bone scans after treatment with sorafenib while having PSA progression. In a later follow-up of that study, median OS was 18 months and progression-free survival (PFS) was <4 months [80].

Sunitinib, a novel multi-tyrosine kinase inhibitor with antiangiogenic properties is being evaluated in CRPC. A phase II study in docetaxel failures demonstrated a median PFS of 19.4 weeks by radiographic and clinical evaluation and radiographic partial response (PR) was documented in 11% of 36 enrolled patients [81]. Biochemical responses were also seen in another phase II study although they did not correlate with clinical or radiographic improvement [82]. Importantly and similar to data with sorafenib, a small phase II study with single-agent sunitinib showed activity in chemotherapy-refractory patients [83]. Nineteen patients received sunitinib continuously at 37.5 mg daily. Biochemical response was demonstrated in 23% of patients. In addition, 1 patient had PR and another 12 showed SD. The drug was well tolerated with manageable expected toxic effects. Given these promising results, a randomized double-blind phase III trial comparing sunitinib plus prednisone with prednisone alone in CRPC patients who have failed docetaxel is currently underway with expected closure in December 2011.

Finally, cediranib is an oral small-molecule inhibitor of receptor tyrosine kinases that influence VEGF. Objective radiographic responses have been demonstrated in CRPC.
patients who failed docetaxel and additional studies are ongoing [84].

**immunomodulatory agents**

While the exact mechanisms by which thalidomide and its analogue lenalidomide demonstrate activity in CRPC are uncertain, their antiangiogenic and immunomodulatory effects likely contribute to their efficacy [85]. Evidence also suggests that lenalidomide inhibits the VEGF-induced PI3-K-Akt pathway signaling contributing to enhanced apoptosis [86]. A small phase II randomized study showed that low-dose thalidomide provides biochemical responses and symptomatic improvement in one-third of enrolled patients, which appeared more effective than higher doses [87]. Subsequently, a randomized phase II study assessed whether the addition of thalidomide would enhance docetaxel’s activity in CRPC [88]. Patients received either docetaxel (30 mg/m² weekly for 3 weeks followed by 1 week of rest) or the same schedule with the addition of thalidomide (200 mg daily). The combination arm showed 53% PSA responses compared with 37% in the docetaxel-alone arm. Importantly, resistance to docetaxel chemotherapy was reversed by adding antiangiogenic agents [89]. In addition, thalidomide was safely and effectively combined with granulocyte–macrophage colony-stimulating factor (GM-CSF) in patients who were hormone naive and in those who had castration-resistant disease [90, 91]. Lenalidomide demonstrated disease stability in 9 of 35 CRPC patients when studied in a phase I study [92]. In addition, a synergistic effect was shown when lenalidomide was paired with paclitaxel in patients with CRPC receiving prior taxanes although the optimal dosing schedule remained unclear [93]. A single-agent phase II trial in chemotherapy-naive CRPC showed that 38% of treated patients had a PSA response and that PSA doubling time improved in responding patients. Furthermore, 63% of patients showed SD radiographically that lasted a median of 8 months [94]. Of importance, lenalidomide was safely combined with docetaxel; such combination proved effective in patients with chemotherapy-naive disease and in chemotherapy failures [95]. Of 31 assessable patients in a phase I study combining lenalidomide with docetaxel, 15 had biochemical response with >50% PSA decline and 5 patients had PR radiographically. These results led to a phase III trial that is accruing patients to compare docetaxel and prednisone versus the same regimen combined with lenalidomide.

In theory, immunomodulatory agents might have a role in this disease but their optimal utility and dosing remain under investigation.

**immunotherapy**

Given the unique molecules that PCA cells express such as PSA, prostatic acid phosphatase (PAP) and prostate-specific membrane antigen (PSMA), this disease is ideal for exploring immunotherapy techniques because the immune effects of treatment will focus on the prostate tissue and, in theory, not influence surrounding cells. Several immunotherapies are in development in PCA, with variable and multiple targets and varying efficacy (Table 3).

<table>
<thead>
<tr>
<th>Name</th>
<th>Route</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>i.v.</td>
<td>Autologous dendritic cells that are PAP positive, cultured with recombinant PAP linked to GM-CSF; the cells are reinfused to the patient within 2 days; given every 2 weeks for a total of three infusions</td>
</tr>
<tr>
<td>GVAX</td>
<td>Intradermal</td>
<td>Allogenic PCA cells (from LNCaP and PC-3); GM-CSF is secreted locally; given every 2 weeks for 13 doses after initial priming</td>
</tr>
<tr>
<td>PROSTVAC</td>
<td>Intradermal</td>
<td>PSA-targeted poxviral vaccine that expresses co-stimulatory molecules given as a monthly injection starting with a priming dose followed by six monthly boosts</td>
</tr>
<tr>
<td>DCVAX</td>
<td>i.v.</td>
<td>Dendritic cells with PSMA peptides; given as six infusions of autologous dendritic cells pulsed with HLA-A2-specific PSMA peptides (PSM-P1 and PSM-P2) at 6-week intervals</td>
</tr>
</tbody>
</table>

CRPC, castration-resistant prostate cancer; PAP, prostatic acid phosphatase; GM-CSF, granulocyte-macrophage colony-stimulating factor; PCA, prostate cancer; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; HLA, human leukocyte antigen.

**sipuleucel-T**

Sipuleucel-T (Provenge/APC8015) utilizes PAP to target PCA cells by employing autologous dendritic cells as antigen-presenting cells. The agent is constructed by the fusion of the PAP gene to GM-CSF to form a compound that is then loaded ex vivo on to autologous dendritic cells previously harvested by leukapheresis [96, 97]. A phase II placebo-controlled trial of this active immunotherapy enrolled 127 chemotherapy-naive CRPC patients but failed to detect a PFS advantage (11.7 versus 10.0 weeks \( P = 0.052 \)) [98]. However, when an intent-to-treat analysis was carried out, the use of sipuleucel-T improved OS by 4.5 months, a difference that was statistically significant \( P = 0.01 \). Importantly, the treatment was safe, with pyrexia, rigors, tremor, and cold hypersensitivity being the most common adverse events. No patient discontinued treatment due to toxicity, which was of grade 1 or 2 in most patients [98]. Subsequently, a larger phase III study with 512 patients confirmed those findings and confirmed the survival advantage with sipuleucel reducing the risk of death by 22% compared with placebo \( P = 0.032 \), leading to its recent Food and Drug Administration (FDA) approval [99]. In addition, an integrated analysis of the two phase III trials that used this...
immunotherapy proved that the witnessed survival advantage was robust and sustained [100]. Despite these positive results, it is important to recognize that enrolled patients were asymptomatic or minimally symptomatic and did not have hepatic or pulmonary involvement. Treated patients with this immunotherapy were highly selected, which might be critical to demonstrate the efficacy advantage. Furthermore, the theoretical possibility of a suboptimal control arm in that phase III study as suggested by some investigators deserves further studies and exploration [101].

**Prostvac**

PROSTVAC is a recombinant virus-based vaccine engineered to express human PSA. Two variations exist; the first is a product of vaccinia virus (rV-PSA) used as a priming agent and the second is a product of fowlpox virus (rF-PSA) used as a boosting agent [102]. Phase I data indicated that the vaccine elicits an immune response, has minimal toxicity, and delays clinical progression [102]. Newer recombinant virus-based vaccines targeting PSA have been combined with a trio of costimulatory molecules (B7.1/CD80, ICAM-1/CD54, and LFA-3/CD58) termed TRICOM that synergize with the viral system (rV-PSA-TRICOM and rF-PSA-TRICOM). Gulley et al. [103] evaluated priming doses of rV-PSA-TRICOM with subsequent monthly boosts of rF-PSA-TRICOM in combination with GM-CSF showing PSA declines. Kantoff et al. [104] reported a randomized phase II study in 125 favorable-risk patients (minimally symptomatic, Gleason score of ≤7) who were assigned to either PROSTVAC plus GM-CSF or control empty vectors plus saline injections. Eighty-two patients received PROSTVAC and 40 received control vectors. While PFS was similar in both groups (P = 0.6), OS was significantly better at 3 years favoring the vaccine approach (25.1 versus 16.6 months for controls), with an estimated hazard ratio of 0.56 (95% confidence interval 0.37–0.85) and stratified log-rank P = 0.0061 [104]. Additional studies alone or in combination along with a confirmatory phase III study are underway [105].

**Other immunotherapy approaches**

DCVax is a second dendritic cell-based vaccine that targets PSA [106]. The vaccine is constructed from autologous dendritic cells pulsed ex vivo with specific PSA peptides that bind to human leukocyte antigen (HLA)-A2. Tjoa et al. [107] proved an immune response against PSA in a preliminary phase I trial. In their follow-up of patients who had either local failure or metastatic disease, responses lasted for up to 149 days in the latter and 187 days in the former [108]. In these studies, each participant received six infusions of autologous dendritic cells pulsed with HLA-A2-specific PSA peptides (PSM-P1 and PSM-P2) at 6-week intervals.

GVAX is a PCA vaccine comprised of two allogenic PCA cell lines that have been genetically modified to secrete GM-CSF [109]. Despite initial enthusiasm, a phase III randomized study comparing GVAX plus docetaxel with docetaxel plus prednisone demonstrated higher mortality in the immunotherapy arm halting the study before complete accrual. The exact reasons of such unexpected results remain to be elucidated [110].

Another immunotherapeutic approach using ipilimumab has shown promise. Ipilimumab is a fully humanized mAb that blocks the T-cell inhibitory receptor CTL-associated antigen-4 (CTLA-4) [111]. A pilot study suggested safety and activity without significant autoimmunity [112]. Importantly, ipilimumab was safely combined with TRICOM immunotherapy with suggested activity in chemotherapy-naive patients [113]. A randomized phase II study of radiotherapy alone or with ipilimumab in chemotherapy-refractory or -naive patients suggested enhanced activity with acceptable tolerance [114]. Finally, a larger phase III study versus placebo in minimally symptomatic CRPC patients who are chemotherapy naive has been initiated.

**Unanswered questions in immunotherapy**

While PSA decline is a common measure for assessing response to any therapeutic intervention in CRPC, immunotherapy used to date does not lead to significant PSA decreases [104, 115]. In addition, the lack of PFS advantage with these agents while having an OS improvement is puzzling. Possible explanation includes delayed beneficial effect for immunotherapy, which can be detected when assessing for survival but would be missed when progression is being evaluated frequently using imaging studies [116]. This may be especially relevant as metrics used for ‘disease progression’ are rather arbitrary. Furthermore, comparing these immunotherapies with placebo might not be appropriate as newer active agents become available, which would question when and how to use these agents. Finally, additional information to explain the negative results of GVAX with docetaxel is eagerly awaited and is of paramount importance. Despite these unanswered questions, the OS benefit with sipuleucel-T has been confirmed suggesting that immunotherapy is a viable treatment option in PCA.

**Therapeutic antibodies**

Using mAbs allows the delivery of cytotoxic agents to malignant cells while avoiding normal tissues. PSMA was identified as an ideal antigenic target in PCA since it is highly restricted to PCA cells and is expressed at high density on the cell membrane [117]. Once antibody–antigen binding takes place, the PSMA–antibody complex is rapidly internalized along with any payload carried by the antibody [117]. Milowsky et al. [118] utilized an yttrium-labeled murine antibody (J 591) against PSMA . In that study, the antibody dose was held constant while the radiation dose was escalated. All observed responses occurred in a dose level higher than the maximum tolerated dose. Using the same antibody, Bander et al. used 177-lutetium-labeled product showing biochemical responses and stability of disease. Other antibodies are also under development [119], but the ideal timing of these agents remains unclear.

**Future directions and challenges**

Our better understanding of the mechanisms leading to CRPC has allowed the development of novel therapeutic agents that avoid much of the toxicity associated with traditional systemic chemotherapy. Although the disease remains incurable, these interventions are likely to improve and prolong survival in
patients suffering from this disease. Once activity is demonstrated in CRPC, additional studies in earlier stage will ensue. In addition, since most patients are unable to tolerate prolonged periods of chemotherapy interventions, utilizing some of these newer agents in the maintenance setting is plausible [120, 121].

Despite the developments on newer therapies, assessing efficacy of noncytotoxic agents remains challenging. While PSA measurements have correlated with activity of chemotherapy, such correlation is lacking with targeted agents. In fact, Dahut et al. [79] showed that patients who respond to sorafenib might demonstrate PSA progression while those who progress biochemically might show radiographic response. The need for adequate surrogate measure is important but until then we should probably rely on radiographic changes as we evaluate newer therapies [122]. Another important challenging task for investigators is identifying the most meaningful end point. While OS is the most important for patients, discrepancies between PFS and OS in some trials require interpretation [99]. Such dichotomy is likely a treatment effect as some newer targeted and immunotherapies have delayed effects that can be missed by carrying out frequent imaging studies that detect early progression.

The identification of several signaling pathways involved in CRPC progression has revolutionized our approach to this disease. Therapeutic strategies being explored in this setting are aimed at identifying the most critical pathway to inhibit its activity. The recent FDA approval of sipuleucel-T in this setting is a testament that immunotherapy has activity in CRPC paving the way for other similar approaches. In addition, the superior activity of denosumab in preventing skeletal-related events when compared with zoledronic acid underscores the understanding of the mechanisms by which bone disease evolves in CRPC [123]. In fact, bone-directed therapies such as alpharadine have demonstrated activity and possible improvement in OS when compared with placebo [124].

Importantly, however, identifying the subset of patients that can benefit from specific therapeutic intervention is paramount to maximize treatment benefits while eliminating unnecessary interventions. The modest benefit demonstrated with EGFR inhibitors in CRPC could be explained by the fact that these agents have demonstrable efficacy in a subset of individuals who carry a specific mutation corresponding to the EGFR gene as seen in lung cancer [125]. It remains unclear whether the same principle applies to CRPC but further studies are warranted. In addition, the lack of bevacizumab activity in CRPC despite the abundance of in vitro data on angiogenesis pathways in the development of CRPC suggests that other pathways might be more important or that bevacizumab might not be the ideal antiangiogenesis agent in this setting. Identifying which pathway is deregulated in a specific patient using molecular studies and microarrays is being investigated to tailor our therapeutic approach [126, 127].

As we move forward, we face the challenges of identifying more critical pathways and understanding how to best utilize these newer therapies. In addition, understanding the best sequence of these new agents is essential as this would ultimately identify therapies that should be moved to earlier disease stages where cure is still possible. While we still face many challenges in treating CRPC, we are certainly moving closer to finding important answers.

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