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Review Article

Current Treatment Strategies for Castration-Resistant Prostate Cancer

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Prostate cancer is the most common cancer in men in United States and the fifth most common cancer in men in Korea. Although the majority of patients with metastatic prostate cancer initially respond to androgen deprivation therapy, almost all patients will eventually progress to develop castration-resistant prostate cancer (CRPC). Treatment options for CRPC remain limited. Prostate cancer was considered unresponsive to chemotherapy until the mid-1990s, when mitoxantrone combined with prednisone was shown to play a role in the palliative treatment of patients with CRPC. In 2004, two large randomized clinical trials demonstrated for the first time a small but significant survival advantage of docetaxel-based chemotherapy compared with mitoxantrone in patients with metastatic CRPC. Recently, cabazitaxel was shown to improve survival in patients with metastatic CRPC who progressed after docetaxel-based chemotherapy. Sipuleucel-T was also demonstrated to improve overall survival in patients with asymptomatic or minimally symptomatic metastatic CRPC. Along with mitoxantrone and docetaxel, cabazitaxel and sipuleucel-T are now approved for use in metastatic CRPC by the US Food and Drug Administration. There have been multiple early-phase clinical trials of various agents for the treatment of CRPC, and some are in phase III development. This review focuses on the key clinical trials of various treatment options of CRPC currently in use and under investigation.

Key Words: *Drug therapy; Immunotherapy; Molecular targeted therapy; Prostatic neoplasms; Survival*

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INTRODUCTION

Prostate cancer is the most common cancer and the second most common cause of cancer-related death in men in United States [1]. In Korea, the incidence of prostate cancer is much lower than in most Western countries. However, it has been rapidly increasing recently [2,3]. Prostate cancer is now the fifth most common cancer in men in Korea [4].

Since the landmark studies of Huggins and Hodges demonstrated the beneficial effects of surgical castration and estrogen administration in patients with metastatic prostate cancer in 1941 [5], androgen deprivation therapy (ADT) has been the mainstay of treatment for metastatic prostate cancer [6-8]. Although the majority of patients with metastatic disease initially respond to ADT, almost all patients will eventually progress after an average of 18 to 24 months, despite maintenance of castrate serum testosterone levels [9]. This clinical condition has been described as androgen-independent or hormone-refractory prostate cancer (HRPC). However, these previously used terms have largely been replaced with castration-resistant prostate cancer (CRPC), with the awareness of the persistent androgen receptor signaling activity despite castrate serum testosterone levels [6,8,10-13]. Treatment options for CRPC remain limited, and the prognosis of patients with CRPC is dismal, with a median survival of 12 to 18 months [9,10]. This review discusses the treatment options of CRPC currently in use and under investigation.

SECONDARY HORMONAL MANIPULATIONS

For patients whose disease progresses after maximal androgen blockade (MAB), antiandrogen may be discontinued in an attempt to achieve antiandrogen withdrawal response. Antiandrogen withdrawal response was initially documented in patients who discontinued flutamide upon the development of CRPC [14]. Antiandrogen withdrawal responses have also been described in patients treated with bicalutamide, nilutamide, megestrol acetate, cyproterone acetate, chlormadinone acetate, diethylstilbestrol (DES), and 13-cis-retinoic acid. Antiandrogen withdrawal results in ≥50% prostate-specific antigen (PSA) reduction in 15% to 30% of patients. The duration of response is brief, with a median duration of approximately 4 months [9,15-17].

Antiandrogen may be switched to an alternative antiandrogen in patients who relapse after initial MAB. In the study by Suzuki et al, antiandrogen withdrawal response was observed in 15.1% of patients who relapsed after initial MAB. Subsequently, second-line MAB was performed by switching to an alternative nonsteroidal antiandrogen (i.e., bicalutamide to flutamide and vice versa). Overall, ≥50% and <50% PSA reductions were observed in 35.8% and 25.4% of patients, respectively, and the overall response duration was more than 202 days [18]. Kassouf et al reported that 64% of patients treated with nilutamide after progression on initial MAB, including flutamide or bicalutamide, experienced PSA reduction, and 29% of patients sustained >50% PSA reduction beyond 3 months [19].

High-dose (150 mg daily) bicalutamide as second-line hormonal therapy resulted in ≥50% PSA reduction in 20% to 45% of patients [20-22]. The most recent study in patients with nonmetastatic CRPC revealed that the median duration of response was 18.5 months in patients with 50% to 85% PSA reduction, and 37.4 months in those with ≥85% PSA reduction [22].

Estrogens may exert their effect by suppressing the hypothalamic-pituitary-gonadal axis and exerting direct cytotoxicity. The most commonly used synthetic estrogen, DES, produces ≥50% PSA reduction in 26% to 66% of patients with CRPC [23,24]. However, its utility is limited due to thromboembolic toxicity, which was not mitigated by low-dose warfarin [25].

Although adrenal androgens, such as dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione, are weak androgens, they retain the potential to stimulate prostate cancer growth in the face of testicular androgen suppression [26]. Ketoconazole inhibits cytochrome P-450 enzyme-mediated steroidogenesis in the testes and adrenal glands. After antiandrogen withdrawal in patients with CRPC, high-dose (1,200 mg/day) and low-dose (600 mg/day) ketoconazole resulted in ≥50% PSA reduction in 27% to 63% and 27% to 46% of patients, respectively [16,27-30].

Several new agents are also being investigated in patients with CRPC. MDV3100 is a pure androgen receptor antagonist that blocks androgen receptor nuclear translocation and DNA binding more effectively than do the currently used androgen receptor antagonists [31,32]. A phase I/II study of MDV3100 in patients with metastatic CRPC showed ≥50% PSA reduction in 56% of patients, and a median time to radiological progression of 47 weeks. The agent was well tolerated and the most common adverse event was fatigue, which generally resolved with dose reduction [32]. A phase III trial comparing MDV3100 versus placebo in patients with docetaxel-refractory CRPC is underway [10,32,33].

Abiraterone acetate is a selective, irreversible, inhibitor of CYP17 essential for androgen biosynthesis. It is 10- to 30-fold more potent than the nonselective inhibitor ketoconazole [10,34]. An early phase I/II and a phase II study demonstrated ≥50% PSA reduction in 67% and 51% of patients, with a median time to PSA progression of 225 days and 169 days in patients with chemotherapy-naïve and post-docetaxel CRPC, respectively [34,35]. In a phase II study of abiraterone acetate plus prednisone in patients with docetaxel-refractory CRPC, ≥50% PSA reduction was observed in 36% of patients, including 45% of ketoconazole-naïve and 26% of ketoconazole-pretreated patients, and the median time to PSA progression was 169 days [36]. An interim analysis of data from a phase III trial (COU-AA-301) comparing abiraterone acetate plus prednisone to prednisone alone in patients with docetaxel-refractory CRPC was recently presented at the 2010 meeting of the European Society for Medical Oncology (ESMO). Abiraterone therapy resulted in significant improvement in overall survival (OS), from 10.4 months to 14.8 months ($p < 0.0001$). It also yielded significant improvement in time to PSA progression (10.2 months vs. 6.6 months; $p < 0.0001$), radiographic progression-free survival (PFS) (5.6 months vs. 3.6 months; $p < 0.0001$), and PSA response rate (29.1% vs. 5.5%; $p < 0.0001$) compared with placebo [37].

SYSTEMIC CHEMOTHERAPY

1. First-line chemotherapy

Prostate cancer was considered unresponsive to chemotherapy until the mid-1990s, when mitoxantrone in combination with prednisone was shown to play a role in the palliative treatment of patients with CRPC [38-41]. A Canadian phase III study in patients with symptomatic CRPC demonstrated that mitoxantrone plus prednisone resulted in significant improvement in palliative response (29% vs. 12%; p=0.01) and duration of palliation (43 weeks vs. 18 weeks; $p < 0.0001$) compared with prednisone alone [41]. The Cancer and Leukemia Group B (CALGB) study in patients with CRPC showed that mitoxantrone plus hydrocortisone delayed time to treatment failure and disease progression with no improvement in OS compared to hydrocortisone alone [42]. In a phase III US Oncology study in patients with asymptomatic CRPC, mitoxantrone plus prednisone achieved a significantly superior outcome in ≥50% PSA reduction (48% vs. 24%; p=0.007), albeit with no

difference in median time to treatment failure, median time to progression, or median survival compared to prednisone alone [43]. Taken together, the effect of mitoxantrone is palliative, with no improvement in OS. Mitoxantrone was approved by the US Food and Drug Administration (FDA) for the palliative treatment of CRPC in 1996, and became the reference therapy for comparison against other regimens [38-40].

In 2004, two randomized clinical trials, the TAX 327 and Southwest Oncology Group (SWOG) 99-16, demonstrated for the first time a survival advantage with docetaxel-based chemotherapy compared to mitoxantrone in patients with metastatic CRPC [44,45].

In the TAX 327 study, patients with metastatic CRPC were randomized to one of three treatment arms: 3-weekly docetaxel, docetaxel weekly for 5 out of every 6 weeks, or control therapy with 3-weekly mitoxantrone. In addition, patients also received oral prednisone daily. The study showed that the median survival of patients treated with 3-weekly docetaxel was significantly longer than that of patients treated with mitoxantrone (18.9 months vs. 16.5 months; p=0.009). Three-weekly docetaxel therapy also yielded significantly superior outcomes with respect to ≥ 50% PSA reduction (45% vs. 32%; $p<0.001$), pain reduction (35% vs. 22%; p=0.01), and improvement in quality of life (22% vs. 13%; p=0.009) compared to mitoxantrone [44].

In the SWOG 99-16 study, patients with metastatic CRPC were randomized to docetaxel plus estramustine or mitoxantrone plus prednisone. Docetaxel plus estramustine therapy resulted in significant improvement in median OS (17.5 months vs. 15.6 months; p=0.02), median time to progression (6.3 months vs. 3.2 months; $p<0.001$), and ≥50% PSA reduction (50% vs. 27%; $p<0.001$) [45].

On the basis of these findings, docetaxel with prednisone therapy for the treatment of metastatic CRPC was approved by the US FDA in May 2004 and is now widely accepted as the standard of care for chemotherapy in patients with CRPC [38-40].

Recently updated data from the TAX 327 study, obtained after extended follow-up, are consistent with previously reported results. The median survival of patients treated with 3-weekly docetaxel was significantly longer than that of patients treated with mitoxantrone (19.2 months vs. 16.3 months; p=0.004). More patients survived ≥3 years in the 3-weekly docetaxel arm than in the mitoxantrone arm (18.6% vs. 13.5%) [46].

Recently, docetaxel has also been combined with other agents to improve efficacy. Capecitabine is an oral fluoropyrimidine preferentially converted to 5-fluorouracil by thymidine phosphorylase in tumor tissues [47-49]. A phase II trial of weekly docetaxel plus capecitabine in patients with CRPC demonstrated ≥50% PSA reduction in 68% to 73% of patients, with a median OS of 17.7 to 22.0 months [47,48]. A phase II trial of 3-weekly docetaxel plus capecitabine in patients with CRPC resulted in ≥50% PSA reduction in 41% of patients, with a median survival of 17 months [49].

Calcitriol (1,25-dihydroxycholecalciferol) is the biologically active form of vitamin D [38]. A single-institution phase II study of docetaxel plus calcitriol in patients with metastatic CRPC demonstrated ≥50% PSA reduction in 81% of patients, with a median time to progression and median survival of 11.4 months and 19.5 months, respectively. [50]. In the randomized phase II Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT), patients with metastatic CRPC were randomized to docetaxel plus calcitriol (DN-101) or docetaxel monotherapy. Docetaxel plus calcitriol therapy did not show statistically significant improvement in ≥50% PSA reduction compared to docetaxel monotherapy (63% vs. 52%; p=0.07), but multivariate analysis demonstrated a lower risk of death (hazard ratio 0.67, p=0.04) [51]. These results led to the initiation of the phase III ASCENT-2 study comparing docetaxel plus calcitriol to docetaxel monotherapy. However, this study was closed early because of an unexpectedly higher death rate in the docetaxel plus calcitriol arm [38].

2. Second-line chemotherapy

Treatment options in patients with CRPC that progresses after docetaxel-based chemotherapy have been limited.

For patients who initially respond to first-line docetaxel-based chemotherapy, re-treatment with docetaxel can be considered [11,52,53]. In the study by Ansari et al, out of 42 patients with metastatic CRPC treated with docetaxel plus prednisone, 10 patients were re-treated with the same regimen as second-line chemotherapy for PSA progression. Of these 10 patients, 7 patients who initially experienced >50% PSA reduction with first-line chemotherapy responded again with >50% PSA reduction with second-line chemotherapy without experiencing a significant increase in hematologic toxicity [52]. In a recently published multicenter study, re-treatment with docetaxel for disease progression in patients who responded initially to first-line docetaxel-based chemotherapy, but discontinued for reasons other than disease progression or unacceptable toxicity, resulted in ≥50% PSA reduction in 48% of patients with a median OS of 16 months. Docetaxel was well tolerated in most patients with 6% grade 3-4 hematologic toxicity [53].

Mitoxantrone can be considered as a second-line chemotherapy in patients with docetaxel-refractory CRPC, but has limited efficacy and poor tolerability. Mitoxantrone resulted in ≥50% PSA reduction in 5.9% to 20% of patients, and a median PSA PFS of between 6.1 weeks and 3.2 months [54-57]. Grade 3-4 neutropenia occurred in 63% of patients [56].

Satraplatin is an orally bioavailable third-generation platinum compound [58,59]. In a phase III study in patients with metastatic CRPC as first-line chemotherapy, satraplatin plus prednisone resulted in a significant increase in PFS (5.2 months vs. 2.5 months; p=0.023), albeit without a significant difference in median OS (14.9 months vs. 11.9 months; p=0.579) compared to prednisone alone [59]. This might be due to the small sample size, because the trial was

closed early by the trial sponsor after 50 of the planned 380 patients were randomized [59,60]. However, the result from the phase III Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial in patients with metastatic CRPC progressing after prior chemotherapy also showed that satraplatin plus prednisone resulted in significant improvement in PFS (11.1 weeks vs. 9.7 weeks; $p < 0.001$), albeit without improvement in median OS (61.3 weeks vs. 61.4 weeks; p=0.80) compared to prednisone alone [60].

Cabazitaxel is a novel tubulin-binding taxane with antitumor activity in docetaxel-refractory cancers [61-63]. In the randomized phase III Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere-Containing Regimen (TROPIC) study, patients with metastatic CRPC who progressed during or after docetaxel-based chemotherapy were randomized to cabazitaxel or mitoxantrone every 3 weeks. In addition, all patients received oral prednisone daily. Cabazitaxel therapy resulted in improved median PFS (2.8 months vs. 1.4 months; $p < 0.0001$), median OS (15.1 months vs. 12.7 months), and lower risk of death (hazard ratio 0.70, $p < 0.0001$) compared to mitoxantrone. The most common grade 3-4 toxicity was neutropenia, which was observed in 82% of patients in the cabazitaxel arm and in 58% of patients in the mitoxantrone arm [64]. Cabazitaxel is the first chemotherapy shown to improve survival in patients with docetaxel-refractory metastatic CRPC. On this basis, it was approved for second-line use in this setting by the US FDA in June 2010.

IMMUNOTHERAPY

Several immunotherapeutic agents for the treatment of prostate cancer have also been investigated.

Sipuleucel-T is an autologous dendritic cell vaccine designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen-presenting cells (APCs), cultured with a recombinant fusion protein (PA2024) composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF) [10,65-67].

The first phase III trial of sipuleucel-T (D9901) in patients with asymptomatic metastatic CRPC did not meet the primary endpoint of time to disease progression (11.7 weeks for sipuleucel-T vs. 10.0 weeks for placebo; p=0.052), but demonstrated improvement in median OS (25.9 months for sipuleucel-T vs. 21.4 months for placebo; p=0.01) [65]. An identically designed phase III trial, D9902A, showed that the median time to disease progression and OS were not significantly different between sipuleucel-T and placebo, although the hazard ratios were in favor of sipuleucel-T [66].

A subsequent phase III Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial of sipuleucel-T in patients with asymptomatic or minimally symptomatic metastatic CRPC shared a similar design to the original trial, but designated OS as the primary endpoint. Treatment with sipuleucel-T resulted in a 4.1-month improvement in median OS (25.8 months vs. 21.7 months), with a 22% relative reduction in the risk of death (hazard ratio 0.78, p=0.03) compared to placebo [67]. These data led to the approval of sipuleucel-T for the treatment of asymptomatic or minimally symptomatic metastatic CRPC by the US FDA in April 2010 [11,63].

GVAX is a cellular vaccine composed of two allogeneic prostate cancer cell lines (LNCaP and PC-3) that is genetically modified to secrete GM-CSF. Phase I and II trials of this vaccine in patients with CRPC demonstrated clinical benefit with limited toxicity [68,69]. On the basis of these early results, two phase III trials, Vaccine Immunotherapy with Allogeneic prostate cancer cell Lines 1 and 2 (VITAL-1 and VITAL-2), were initiated to compare GVAX with conventional therapy for CRPC. In the VITAL-1 trial, GVAX was compared to docetaxel plus prednisone in patients with asymptomatic CRPC. This trial was closed prematurely, when the unplanned futility analysis indicated a $< 30\%$ chance of meeting its predefined primary endpoint of OS improvement. In the VITAL-2 trial, GVAX plus docetaxel was compared to docetaxel plus prednisone in patients with symptomatic CRPC. The VITAL-2 was also terminated early, when an interim analysis revealed more deaths in the GVAX arm than in the control arm [10,70].

PROSTVAC-VF is a cancer vaccine consisting of a recombinant vaccinia vector as a priming immunization with subsequent multiple booster vaccinations, using a recombinant fowlpox vector. Both vectors contain the transgenes for PSA and a triad of T-cell co-stimulatory molecules called TRICOM, including B7.1, intercellular adhesion molecule-1 (ICAM-1), and leukocyte function-associated antigen-3 (LFA-3) [70,71]. A phase I trial of PROSTVAC-VF in patients with CRPC showed PSA stabilization in 40% of patients and limited toxicity [72]. A phase II trial of PROSTVAC-VF in patients with minimally symptomatic metastatic CRPC did not meet the primary endpoint of PFS, but achieved an 8.5 month improvement in median OS (25.1 months for PROSTVAC-VF vs. 16.6 months for controls), and a 44% reduction in the death rate (hazard ratio 0.56, p=0.0061) at 3 years post-study [73]. A phase III trial of PROSTVAC-VF is planned [70,73].

TARGETED THERAPY

1. Endothelin receptor antagonists

Atrasentan is a selective endothelin A (ET_A) receptor antagonist with an 1,800-fold greater affinity for ET_A than ET_B [74]. A phase III trial of atrasentan in patients with metastatic CRPC showed that atrasentan did not improve time to disease progression (hazard ratio 0.89, p=0.136) or OS (hazard ratio 0.97, p=0.775) compared to placebo [75]. The second phase III trial of atrasentan in patients with nonmetastatic CRPC demonstrated lengthening of PSA doubling time (p=0.031), and slowing of bone alkaline phosphatase increment ($p < 0.001$) compared to placebo, but did

not meet the primary endpoint of time to disease progression (p=0.288) [76]. A phase III trial of docetaxel with or without atrasentan in patients with metastatic CRPC is ongoing [10,76].

Zibotentan (ZD4054) is a specific ET_A receptor antagonist with no detectable binding to the ET_B receptor [74,77,78]. Recently, the final analysis of the phase II trial of zibotentan in patients with asymptomatic or mildly symptomatic metastatic CRPC was reported [77]. Consistent with previous analyses [78], zibotentan therapy did not meet the primary endpoint of time to progression. Although the difference in OS between the zibotentan and placebo arms had decreased compared to the previous analyses, zibotentan therapy continued to suggest an OS advantage (23.5 months for zibotentan 10 mg, 23.9 months for zibotentan 15 mg vs. 19.9 months for placebo; p=0.254, p=0.103, respectively) [77]. Three phase III Zibotentan Endothelin A Use (ENTHUSE) trials are ongoing in patients with CRPC [74].

2. Angiogenesis inhibitors

Bevacizumab is a recombinant humanized monoclonal antibody with anti-angiogenic activity through blockade of vascular endothelial growth factor (VEGF) [79]. The phase II, CALGB 90006 study in chemotherapy-naïve metastatic CRPC patients showed that the combination of docetaxel, estramustine, and bevacizumab resulted in >50% PSA reduction in 75% of patients, and partial response in 59% of patients, with a median OS of 24 months [80]. In a phase II study in patients with docetaxel-refractory CRPC, bevacizumab plus docetaxel resulted in ≥50% PSA reduction in 55% of patients, and partial response in 37.5% of patients, with a median OS of 9 months [81]. In the phase III, CALGB 90401 study, chemotherapy-naïve metastatic CRPC patients were randomized to docetaxel plus prednisone in combination with either bevacizumab or placebo. The results were recently presented at the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting, but disappointingly, the addition of bevacizumab to docetaxel plus prednisone did not improve median OS (22.6 months for the experimental arm vs. 21.5 months for the control arm; hazard ratio 0.91, p=0.181) [82].

Thalidomide is also an angiogenesis inhibitor. In a phase II trial of thalidomide in patients with metastatic CRPC, ≥50% PSA reduction was observed in 18% of patients treated with low-dose thalidomide (200 mg/day), but in none of the patients treated with high-dose thalidomide (1,200 mg/day) [83]. In a phase II trial comparing weekly docetaxel plus thalidomide versus docetaxel monotherapy in patients with metastatic CRPC, the addition of thalidomide resulted in a higher ≥50% PSA reduction rate (53% vs. 37%; p=0.32) and improvement in median OS (28.9 months vs. 14.7 months; p=0.11) compared to docetaxel monotherapy [84].

In a subsequent phase II trial in patients with metastatic CRPC, the efficacy of the combination of bevacizumab, thalidomide, docetaxel, and prednisone was evaluated. The combination of these drugs resulted in ≥50% PSA reduction in 89.6% of patients, with a median time to progression and median OS of 18.3 months and 28.2 months, respectively [85].

3. Tyrosine kinase inhibitors

Small molecule tyrosine kinase inhibitors (TKIs) have also been studied in prostate cancer.

In the first stage of a phase II trial of sorafenib, 22 patients with metastatic CRPC were enrolled. Fifty-nine percent of patients had received prior docetaxel or mitoxantrone. Sorafenib therapy failed to show >50% PSA reduction. However, discordance between PSA progression and improvement in metastatic lesions on bone scan was observed in 2 patients [86]. In the second stage of the trial, 24 additional patients with metastatic CRPC were enrolled. Eighty-eight percent of patients had received prior docetaxel. Of the 24 patients, 1 patient experienced partial response and 10 patients attained stable disease. The median PFS and median OS were 3.7 months and 18.0 months, respectively. Pooled data from both stages of the trial for all 46 patients demonstrated a median OS of 18.3 months [87]. Another phase II study included 57 chemotherapy-naïve CRPC patients. Out of 55 evaluable patients, 2 patients experienced >50% PSA reduction and 15 patients attained stable disease (4 according to RECIST and 11 according to PSA-based criteria) [88]. A third phase II trial that included 28 patients with chemotherapy-naïve CRPC showed ≥50% PSA reduction in 1 patient (3.6%). However, PSA reduction was observed in 10 out of 16 patients who discontinued sorafenib therapy, which suggested that sorafenib may affect PSA production or secretion independently of its antitumor activity [89].

A phase II study of sunitinib in patients with chemotherapy-naïve (n=17) or docetaxel-refractory (n=17) CRPC revealed >50% PSA reduction in 1 patient per treatment group. However, as for the patients in the sorafenib trial, assessments of radiologic disease status were often discordant with PSA changes [90]. Another phase II study of sunitinib in patients with metastatic CRPC whose disease progressed following one to two chemotherapy regimens, including docetaxel, showed that sunitinib therapy resulted in ≥50% PSA reduction in 12.1% of patients, ≥30% reductions in the size of measurable disease by RECIST criteria in 11.1% of patients, a reduction in pain score of ≥2 points in 13.6% of patients, and a median PFS of 19.4 weeks. Severe grade 3-4 toxicities were infrequent, but drug discontinuation due to toxicities occurred in 52.8% of patients [91]. The phase I/II trial of sunitinib in combination with docetaxel and prednisone resulted in PSA response in 56% of patients, a median time to PSA progression of 42.1 weeks, and a partial response of measurable disease in 39% of patients. The most common grade 3-4 adverse events were neutropenia (75%), febrile neutropenia (15%), and fatigue (15%) [92]. A phase III trial comparing sunitinib plus prednisone versus prednisone alone in patients with docetaxel-refractory metastatic CRPC is underway. The pri-

mary endpoint of this trial is OS [90,93].

CONCLUSIONS

The combination of docetaxel and prednisone is currently accepted as the standard first-line chemotherapy for patients with CRPC and has been approved by the US FDA. Recently, sipuleucel-T and cabazitaxel have been shown to improve OS in patients with asymptomatic or minimally symptomatic metastatic CRPC and in patients with docetaxel-refractory metastatic CRPC, respectively, and both drugs have been approved by the US FDA. However, the survival benefit of these drugs in CRPC is modest, and more efficacious drugs and drug combinations need to be developed. Although various agents appear promising for the treatment of CRPC in early-phase clinical trials, adequately powered randomized phase III trials will be required to validate these findings.

Conflicts of Interest

The authors have nothing to disclose.

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