

Novel strategies in the treatment of castration-resistant prostate cancer (Review)

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Abstract. Prostate cancer is the most common cancer in men in Europe and the United States, and the third leading cause of death from cancer in Europe. Survival of prostate cancer cells is dependent on the activation of androgen receptors (AR), that are overexpressed in this tumor. Furthermore, ~90% of prostate cancer patients that respond to first-line androgen deprivation therapy (ADT) undergo rapid progression. This condition is defined as castration-resistant prostate cancer (CRPC). Docetaxel-based regimens significantly improve overall survival (OS) in patients with CRPC and represent the only treatment strategy approved by the Food and Drug Administration (FDA). Recently, abiraterone (second hormonal therapy) and cabazitaxel (new taxane) have been shown to improve survival in patients with CRPC who progressed following docetaxel-based chemotherapy. Vaccine therapy has also been demonstrated to improve OS in patients with asymptomatic or minimally symptomatic metastatic CRPC. Additional therapeutic targets have been analyzed in prostate cancer, including apoptosis, angiogenic receptors, vitamin D and Src pathways. Several phase II studies are ongoing. The high frequency of prostate cancer-related metastatic bone disease has led to consider this pathway as a therapeutic target. To this end, several bone-targeted agents have been investigated, most notably zoledronic acid, which is highly effective at stabilizing the bone and preventing skeletal complications. More recently, a nuclear factor- β ligand (RANKL) inhibitor, denosumab, has been developed for the treatment of bone metastases.

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1. Introduction

Cancer of the prostate is the leading type of cancer and the second cause of cancer-related deaths among men in Europe and the USA (1). Most patients have a low-risk, clinically localized disease at diagnosis and can be treated effectively with surgery and radiation (2,3). However, ~10-20% of patients are diagnosed with locally advanced or metastatic disease and an additional, sizable proportion will progress despite surgery and radiation (3,4). Thus, advanced prostate cancer remains a significant treatment challenge.

The mainstay of treatment for metastatic prostate cancer is androgen deprivation therapy (ADT), such as luteinizing hormone-releasing hormone (LHRH) agonists, anti-androgen and their combination, named maximal androgen blockade (MAB) (5-7). Although the majority of patients with metastatic disease initially respond to hormonal therapy, almost all of them will eventually progress after an average 18-24 months, despite maintenance of castrate serum testosterone levels <50 ng/ml (8). Castration-resistant prostate cancer (CRPC) presentation subtypes include biochemical progression prostate-specific antigen (PSA >4 ng/ml), clinical and/or symptomatic progression, or both (biochemical first). In patients with CRPC, treatment options are based on the addition of anti-androgens, if they had been previously treated with LHRH agonists; the addition of LHRH agonists, if they had been previously given anti-androgens; or anti-androgen withdrawal for those previously treated with MAB. Response to anti-androgen withdrawal was initially observed in patients who discontinued flutamide upon the development of CRPC (9). After secondary hormonal treatment, most patients will progress within several years (10), and effective treatment options for CRPC remain limited.

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In the late 1990s, chemotherapy with mitoxantrone-based regimens was shown to provide some palliative benefits in CRPC (11,12), although no therapy has been shown to improve OS. The most dramatic shift in the treatment paradigm came in 2004, with the demonstration in the trials named TAX 327 and South Western Oncology Group (SWOG) 9916 that docetaxel-based chemotherapy provides a significant survival benefit in patients with CRPC (4,13). This has led to a significant expansion of the role of chemotherapy in the management of prostate cancer, which is now being investigated in the management of locally advanced hormone-sensitive disease. Furthermore, novel targeted therapies targeting several pathways in prostate cancer cells are under investigation.

2. Systemic chemotherapy

It was considered for the treatment of prostate cancer only in mid-1990s. Mitoxantrone, in combination with prednisone, was shown to play a role in the treatment of patients with CRPC (12,14-16). A Canadian phase III study in patients with symptomatic CRPC demonstrated that, compared to prednisone alone, this combination resulted in a significant improvement in both response rate (29% versus 12%; $p=0.01$) and duration of palliation (43 versus 18 weeks; $p<0.0001$) (12). In a phase III US Oncology study in patients with asymptomatic CRPC, mitoxantrone plus prednisone induced a significantly superior outcome in $\geq 50\%$ PSA reduction (48% versus 24%; $p=0.007$), albeit with no difference in median time to treatment failure, median time to progression, or median survival (17). Although unable to achieve an improvement in OS, mitoxantrone was approved by the US Food and Drug Administration (FDA) for the palliative treatment of CRPC in 1996 (14-16).

In 2004, two randomized clinical trials (TAX 327 and SWOG 9916) demonstrated for the first time a survival advantage with docetaxel-based chemotherapy compared to mitoxantrone in patients with metastatic CRPC (4,13). In the TAX 327 study, patients with metastatic CRPC were randomized to one of the following treatment arms: i) thrice-weekly docetaxel; ii) docetaxel weekly for 5 out of every 6 weeks; iii) control therapy with thrice-weekly mitoxantrone. The study showed that the median survival of patients treated with thrice-weekly docetaxel was significantly longer than that of patients treated with mitoxantrone (18.9 vs. 16.5 months; $p=0.009$). Also, this schedule yielded significantly superior outcomes with respect to $\geq 50\%$ 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 (4). In the SWOG 9916 study, patients with metastatic CRPC were randomized to receive docetaxel plus estramustine or mitoxantrone plus prednisone. Docetaxel plus estramustine therapy resulted in significant improvement in median OS (17.5 vs. 15.6 months; $p=0.02$), median time to progression (TTP) (6.3 vs. 3.2 months; $p<0.001$), and $\geq 50\%$ PSA reduction (50% vs. 27%; $p<0.001$) (13).

Based on these results, thrice-weekly docetaxel with prednisone therapy was approved by the FDA for the treatment of metastatic CRPC in May 2004 and is now widely accepted as the standard of care for chemotherapy in patients with CRPC (14-16). A recent update of the TAX 327 study, stemmed from an extended follow-up, is consistent with previously reported results. The median survival of patients treated with thrice-

weekly docetaxel was significantly longer than that of patients treated with mitoxantrone (19.2 vs. 16.3 months; $p=0.004$). More patients survived ≥ 3 years in the thrice-weekly docetaxel arm than in the mitoxantrone arm (18.6 vs. 3.5%) (18). This improved OS shown by the updated results was ascribed to an initial bias, due to the great crossover into the thrice-weekly docetaxel arm.

3. Agents under development

Agents under development in clinical, ongoing studies are summarized in Table I.

Hormonal therapy. Disease progression despite effective ADT is a significant event in the natural history of prostate cancer (4,13,19). Currently available anti-androgen therapies, that are often used with LHRH agonists, include flutamide, bicalutimide, and nilutimide. These drugs exhibit only moderate binding affinity for the androgen receptors (AR) (20), and this is a limiting factor for their therapeutic efficacy. Since they do not blockade the adrenal androgen production, specific inhibitors of adrenal androgen synthesis have been developed.

Abiraterone acetate (CB7630) is a potent, orally bioavailable, small molecule inhibitor of cytochrome P17, which catalyses two key reactions (17- α -hydroxylase and 17,20 xylase) involved in androgen biosynthesis (21), thereby dramatically reducing both adrenal and intra-tumoral androgen production. A phase I/II study of abiraterone (at dose of 1,000 mg/day) in 54 patients with CRPC showed a 67% reduction in serum PSA level and a 37.5% partial response. These results clearly support the hypothesis that CRPC remains sensitive to endocrine therapy in most patients, and show that abiraterone is a promising agent for the treatment of CRPC (22). Based on these results, a phase III trial (NCT00638690) in patients previously treated with 1 or 2 chemotherapy regimens, one of which contained docetaxel, has recently completed enrolment of 1,195 patients, comparing the efficacy and safety of abiraterone acetate plus prednisone versus placebo plus prednisone. Patients were allowed to receive treatment until documented disease progression (of all 3 types, namely: PSA progression, radiographic progression and symptomatic or clinical progression) or unacceptable toxicity. Primary efficacy endpoint is OS, whereas secondary endpoints are PSA response rate, time to PSA progression and radiographic progression-free survival (R-PFS) (23,24). Ad interim analysis has shown an improvement in OS (14.8 vs. 10.9 months; $p<0.0001$, HR=0.64), PSA response rate (38 vs. 10.1%; $p<0.0001$), time to PSA progression (10.2 vs. 6.6 months; $p<0.0001$), R-PFS (5.6 vs. 3.6 months; $p<0.0001$). Adverse events, more frequent in the Abiraterone arm, were fluid retention (30.5 vs. 22.3%), hypokalemia (17.1 vs. 8.4%) and cardiac disorders (12.5 vs. 10.4%). Grade 3 and 4 hypokalemia was observed in 3.8% of the Abiraterone group versus 0.8% of the placebo group. Grade 3 and 4 hypertension was observed in 1.3 vs. 0.3% of the placebo group (25).

Other chemotherapy agents. The demonstration that chemotherapy can, indeed, improve survival in this patient population and to an extent similar to that seen in other chemotherapy-sensitive tumor types has challenged the notion that CRPC is chemotherapy refractory and enhanced the efforts to develop more effective chemotherapy regimens and assess the possi-

Table I. Selected agents under development for castration-resistant prostate cancer.

Drug	Mechanism of action	Study design	FDA approval
Hormonal therapy			
Abiraterone	Inhibitor of cytochrome p17	Phase III	Yes (US FDA)
Other chemotherapy agents			
Cabazitaxel	Microtubule inhibitor	Phase III	Yes (US FDA)
Satraplatin	Binds to the DNA's cancer cells	Phase III	No
Vaccines			
Sipileucel	Elicit an immune response against cancer cells carrying the PAP antigen	Phase III	Yes (US FDA)
GVAX	Activate dendritic cells expressing GM-CSF	Phase II	-
PROSTVAC-VF	Stimulate T-cell responses expressing PSA sequence which alteration in HLA-A2 epitope	Phase III	No
Anti-apoptotic agents			
Oblimersen	bcl-2 antisense oligonucleotide	Phase II	-
Angiogenesis inhibitors			
Bevacizumab	Anti-VEGF inhibitor	Phase III	No
Aflibercept	Anti-VEGF inhibitor	Phase III	No
Tyrosine kinase inhibitors			
Dasatinib	Src-inhibitor	Phase III	No
Sorafenib	Inhibitor of Raf kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-B, c-Kit, FLT-3, RET	Phase II	-
Sunitinib	Inhibitor of VEGFR 1-3, PDGFR α - β , c-Kit, FLT3, RET	Phase II	-
Vitamin D analogues			
Calcitriol	Inhibits proliferation and stimulates apoptosis activating VDR-RXR complex	Phase III	No
Endothelin receptor antagonists			
Atrasentan	Anti-ETA and ETB receptors	Phase III	No
Zibotentan	Anti-ETA receptors	Phase III	No

PDGFR, platelet-derived growth factor receptor; VDR, vitamin D receptor; RXR, retinoic acid X receptor.

bility of a second-line therapy. To overcome the emergence of taxane resistance (26,27), a new semi-synthetic taxane, cabazitaxel (XRP6258), was tested in preclinical and clinical studies. It has been shown to exert similar efficacy compared with docetaxel against sensitive cell lines and tumor models, in that it was active against tumor cells/models resistant to currently available taxanes and was more potent than docetaxel against multidrug resistance transporter (MDR-1)-expressing tumor cells resistant to taxanes (27,28).

In the randomized phase III treatment of hormone-refractory metastatic prostate cancer previously treated with a taxotere-containing regimen (TROPIC) study, 755 patients with metastatic CRPC, who progressed during or after docetaxel-based chemotherapy, were randomized to receive cabazitaxel (25 mg/m² thrice-weekly) or mitoxantrone every 3 weeks, with the addition of oral prednisone daily. Cabazitaxel therapy resulted in improved median progression-free survival

(PFS) (2.8 vs. 1.4 months: $p < 0.0001$), median OS (15.1 vs. 12.7 months: $p < 0.0001$) compared to mitoxantrone. Cabazitaxel has demonstrated an improvement in tumor assessment (response rate 14.4 vs. 4.4%: $p < 0.0005$, HR=0.64), PSA reduction (39.2 vs. 17.8%: $p < 0.0002$), pain control (9.2 vs. 7.8%: $p < 0.6286$). The most common grade 3-4 toxicities were neutropenia, which was observed in 82% of patients in the cabazitaxel arm compared with 58% of patients in the mitoxantrone arm and diarrhea grade 3-4 (6.2% in cabazitaxel arm versus 0.3% in mitoxantrone arm) (29). Total deaths during the study were similar in America (0.9% in cabazitaxel arm versus 0.8% in mitoxantrone arm: $p < 0.0001$, HR=0.72), whereas it was superior in the cabazitaxel group in Europe (4.9 vs. 3.0%: $p < 0.0001$, HR=0.72). A European revision (30) of the hazard ratio by country group analysis showed that in countries other than American and European countries the higher number of deaths was correlated to an inadequate management of grade 3-4 adverse events in

respect of American Society of Clinical Oncology (ASCO) guidelines, such as delayed dose reduction of cabazitaxel. Overall, cabazitaxel determined a 28% reduction of death risk ($p < 0.0001$, HR=0.72). On this basis, it was approved for second-line use in this setting by the US FDA in June 2010.

Satraplatin (JM216) is an orally bioavailable third-generation platinum compound (31,32), that has shown activity against CRPC cell lines and taxane-resistant cell lines *in vitro*. It appears as a good candidate for use in CRPC after failure of docetaxel (33). Results from a prematurely terminated, randomized, phase III trial combining satraplatin with prednisone as first-line therapy for CRPC suggested that it has promising antitumor activity compared with prednisone alone (32), and this led to a randomized, placebo-controlled, phase III trial of this regimen as second-line therapy. The Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial enrolled 950 patients unresponsive to prior chemotherapy (51% had received prior docetaxel): patients were randomized to receive satraplatin (80 mg/m² x 5 days, q5 weeks) plus prednisone or prednisone plus placebo (34). The primary endpoint was PFS, defined by radiological progression, symptomatic progression (i.e. increased pain or need for bone radiation), skeletal events, or death. This study showed a highly significant improvement in PFS ($p < 0.001$, HR=0.69) and pain progression ($p < 0.001$, HR=0.67). In addition, patients in the satraplatin arm had a 25% PSA response rate, a 7% objective tumor response rate, and a 24% pain response rate, which were all significantly better than with prednisone alone (12, 1, and 14%, respectively) (34). However, due to the evidence of no OS benefit, satraplatin was not approved by the FDA.

Immunotherapy. Several immunotherapeutic agents have been investigated for the treatment of prostate cancer. 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, cultured with a recombinant fusion protein (PA2024) composed of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor (GM-CSF) (35-38). The first phase III trial of sipuleucel-T (D9901) in patients with asymptomatic metastatic CRPC did not meet the primary endpoint of TTP (11.7 for sipuleucel-T versus 10 weeks for placebo: $p = 0.052$), but demonstrated improvement in median OS (25.9 for sipuleucel-T versus 21.4 months for placebo: $p = 0.01$) (36). 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 vs. 21.7 months), with a 22% relative reduction in the risk of death ($p = 0.03$, HR=0.78) compared to placebo (38). 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 (39,40).

Other vaccine therapies with GVAX (cellular vaccine composed of two allogeneic prostate cancer cell lines, namely LNCaP and PC-3) showed in phase I and II trials more deaths in the GVAX arm than in the control arm and were obviously prematurely closed.

PROSTVAC-VF, consisting of a recombinant vaccinia vector as a priming immunization with subsequent multiple booster vaccinations, was examined in a phase II trial and did not meet the primary endpoint of PFS, but achieved an 8.5 month improvement in median OS (25.1 for PROSTVAC-VF versus 16.6 months for controls), and a 44% reduction in the death rate ($p = 0.006$, HR=10.56) at 3 years post-study (41). A phase III trial of PROSTVAC-VF has been planned but not yet carried out (41,42).

Targeted therapy. Given the recent success of chemotherapy for the treatment of CRPC, there is a strong rationale to incorporate targeted agents into established regimens in an effort to further improve clinical outcomes. Mostly, targeted agents are combined with chemotherapy, similar to the approach taken in other solid tumors, but the value of this approach has yet to be shown in CRPC, and several important questions remain unanswered.

Anti-apoptotic agents. Bcl-2 overexpression, which is observed in a high percentage of patients with CRPC, prevents apoptosis and has a critical role in the transition from androgen-dependent to androgen-independent tumor growth (43). This protein contributes to resistance to docetaxel. For this reason, a phase II study investigated the activity of oblimersen sodium, a bcl-2 antisense oligonucleotide, administered before docetaxel to patients with CRPC. Chemotherapy-naïve patients with prostate-specific antigen (PSA) progression and testosterone ≤ 0.5 ng/ml received docetaxel 75 mg/m² on day 1 or oblimersen 7 mg/kg/day by continuous i.v. infusion on days 1-7 with docetaxel 75 mg/m² on day 5 every 3 weeks for 12 cycles. PSA response was observed in 46% and 37% of 57 and 54 patients treated with docetaxel and docetaxel-oblimersen, respectively. Partial response according to RECIST criteria was achieved in 18 and 24%, respectively. Oblimersen added to docetaxel was associated with an increase in the incidence of grade ≥ 3 fatigue, mucositis, and thrombocytopenia. Major toxic events were reported in 22.8 and 40.7% of patients with docetaxel and docetaxel-oblimersen, respectively (44).

Angiogenesis inhibitors. Angiogenesis inhibitors appear to have potential usefulness in the treatment of prostate cancer, as they do in many other solid tumors, because angiogenesis and lymphangiogenesis play important roles in the process of tumor progression and metastasis (45). Microvessel density and plasma vascular endothelial growth factor (VEGF) levels are both independent prognostic factors in prostate cancer (46,47) and, in addition to stimulating neovascularization of the tumor, there is evidence to suggest that tumor-derived VEGF may directly stimulate tumor growth via activation of VEGFRs expressed on tumor cells (48,49). Several classes of anti-angiogenic agents are being investigated in prostate cancer (49).

Bevacizumab is a recombinant humanized monoclonal antibody with anti-angiogenic activity through blockade of VEGF (50,51). The phase II, CALGB 90006 study, in chemotherapy-naïve metastatic CRPC patients showed that the combination of docetaxel, estramustine, and bevacizumab is able to induce $>50\%$ PSA reduction in 75% of patients, and a partial response in 59% of patients, with a median OS of 24 months (52). In a phase II study in patients with docetaxel-refractory CRPC, bevacizumab plus docetaxel resulted in $\geq 50\%$ PSA reduction in 55% of patients, and a partial response in 37.5% of patients,

with a median OS of 9 months (53). In the phase III, CALGB 90401 study, chemotherapy-naïve metastatic CRPC patients were randomized to receive docetaxel plus prednisone in combination with either bevacizumab or placebo. The results were recently presented at the 2010 ASCO Annual Meeting but, disappointingly, the addition of bevacizumab to docetaxel plus prednisone did not improve median OS (22.6 for the experimental arm versus 21.5 months for the control arm: $p=0.181$, $HR=0.91$) (54).

Aflibercept (VEGF Trap) is a recombinant fusion protein consisting of the human VEGF extracellular domain fused to the Fc domain of an IgG antibody. It has a higher affinity for VEGF than bevacizumab *in vitro* (55). Aflibercept has shown promising activity in combination with various chemotherapy regimens for the treatment of advanced solid tumors (primarily colorectal, breast, and ovarian cancer) and is currently being investigated in combination with standard docetaxel/prednisone for the first-line treatment of metastatic CRPC. This randomized, placebo-controlled, phase III trial (VENICE; NCT00519285) will enrol 1,200 patients, and OS is the primary endpoint (56).

Tyrosine kinase inhibitors. Small molecule tyrosine kinase inhibitors (TKIs) have also been studied in prostate cancer, including dasatinib, sorafenib, and sunitinib. Several trials are ongoing.

The most promising TKI is dasatinib, that targets Src pathways (49). Src is overexpressed in prostate cancer, and correlates with disease progression (57). Dasatinib inhibits proliferation, cell adhesion, migration and invasion of prostate cancer cells *in vitro* (58). A phase II study CA180085 investigating the activity of dasatinib in patients with metastatic CRPC has been started (59). The primary endpoint is the composite response/stable disease (SD) rate, achieved in 13 of 47 (28%) patients with 95% confidence interval above the minimum anticipated response rate of 10%. The secondary endpoint (lack of progression by both Response Evaluation Criteria In Solid Tumors (RECIST) and bone scan analysis) was met by 43% and 19% of patients on week 12 and 24, respectively. Thus, dasatinib may have a future role for patients with prostate cancer as both anti-tumor and bone-targeted agent. A randomized ongoing double-blind phase III trial comparing docetaxel combined with dasatinib to docetaxel combined with placebo (READY Trial) is presently open in 1,380 patients with metastatic CRPC. Its purpose is to determine whether OS can be prolonged in patients who receive dasatinib in addition to the standard docetaxel plus prednisone regimen (60).

Vitamin D analogues. Vitamin D receptor is implicated in several pathways in prostate cancer cells, principally in the regulations of cell differentiation and proliferation. Phase I studies have demonstrated that the use of vitamin D analogues is able to induce inhibition of proliferation and stimulates apoptosis in prostate cancer cells (61). A single-institution phase II study of docetaxel plus calcitriol in patients with metastatic CRPC demonstrated $\geq 50\%$ PSA reduction in 81% of patients, with a median time to progression and median survival of 11.4 and 19.5 months, respectively (62). In the randomized phase II Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT), patients with metastatic CRPC were randomized to receive docetaxel plus calcitriol (DN-101) or docetaxel monotherapy. Docetaxel

plus calcitriol therapy did not show statistically significant improvement in $\geq 50\%$ PSA reduction compared to docetaxel monotherapy (63 vs. 52%; $p=0.07$), but multivariate analysis demonstrated a lower risk of death ($p=0.004$, $HR=0.67$) (63). These results led to the initiation of the phase III ASCENT-2 study comparing docetaxel plus high dose calcitriol to docetaxel monotherapy. However, this study was closed early because of an unexpectedly higher death rate in the docetaxel plus calcitriol arm (64).

Endothelin receptor antagonists. Atrasentan is a selective endothelin A (ETA) receptor antagonist with a 1,800-fold greater affinity for ETA than ETB (65). A phase III trial of atrasentan in patients with metastatic CRPC showed that atrasentan did not improve time to disease progression ($p=0.136$, $HR=0.89$) or OS ($p=0.775$, $HR=0.97$) compared to placebo (66). The second phase III trial of atrasentan in patients with non-metastatic 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 improvement ($p=0.288$) (66). A phase III trial of docetaxel with or without atrasentan in patients with metastatic CRPC is ongoing (35,67).

Zibotentan (ZD4054) is a specific ETA receptor antagonist with no detectable binding to the ETB receptor (65,68,69). Recently, the final analysis of the phase II trial of zibotentan in patients with asymptomatic or mildly symptomatic metastatic CRPC was reported (68). Consistent with previous analyses (69), zibotentan therapy did not meet the primary endpoint of time to progression. Although the difference in OS between the zibotentan and placebo arms was found to be decreased compared to the previous analyses, zibotentan therapy resulted in an OS advantage (23.5 for zibotentan 10 mg, 23.9 months for zibotentan 15 mg vs. 19.9 months for placebo: $p=0.254$ and $p=0.103$, respectively) (68). Three phase III Zibotentan Endothelin A Use (ENTHUSE) trials are ongoing in patients with CRPC (65).

Bone-targeted agents. Up to 75% of advanced prostate cancer patients develop bone metastases (70). Bone metastases lead to osteoclast-mediated bone destruction and clinical consequences include skeletal-related events (SREs) (71,72). Prostate cancer cells secrete osteogenic growth factors, activating osteoblasts to deposit new bone matrix; osteoblasts secrete a range of additional factors such as fibroblast growth factor, that attract prostate cancer cells, further enhancing their proliferation. RANKL-secreting osteoblasts can activate osteoclasts, leading to bone resorption. For that reason, several bone-targeted agents have been developed, most notably bisphosphonates, which are highly effective at stabilizing the bone and preventing skeletal complications (73-75).

In a multicenter, placebo-controlled phase III trial, 643 patients with metastatic CRPC were randomly assigned to receive intravenous zoledronic acid (4 mg) or placebo, every 3 weeks for 15 months (core phase), with an option to continue for an additional 9-month extension phase (total study time: 24 months). The primary efficacy endpoint was the proportion of patients having at least one SRE, which was prospectively defined as a pathologic fracture, spinal cord compression, radiation therapy or surgery to bone, or change in the anti-neoplastic therapy to treat bone pain. Zoledronic acid reduced the incidence of SREs (38 vs. 49%; $p=0.028$), and the annual

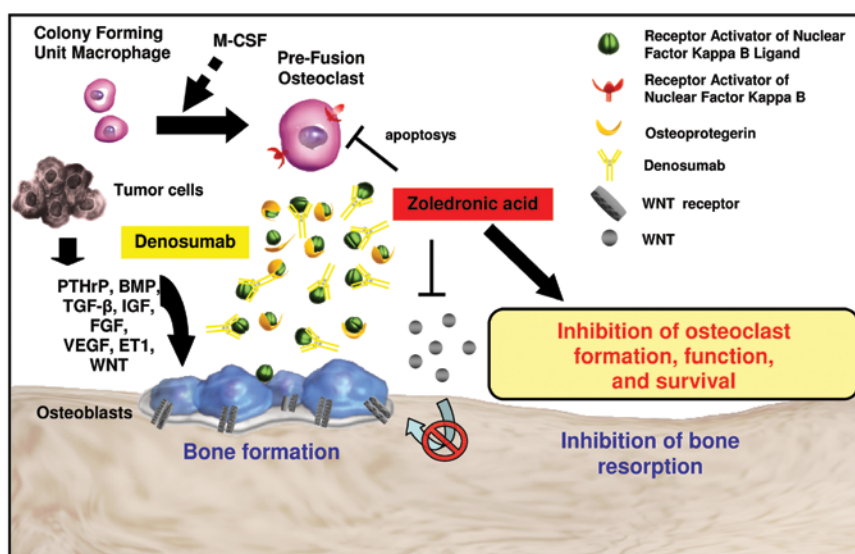


Figure 1. Possible mechanism of action of zoledronic acid and denosumab.

incidence of SREs was 0.77 for the zoledronic acid group versus 1.47 for the placebo group ($p=0.005$). The median time to the first SRE was 488 days for the zoledronic acid group versus 321 days for the placebo group ($p=0.009$). Compared with placebo, zoledronic acid reduced the ongoing risk of SREs by 36% ($p=0.002$, $RR=0.64$). Patients in the zoledronic acid group had a lower incidence of SREs than did patients in the placebo group, regardless of whether they had an SRE prior to entry in the study. Long-term treatment with zoledronic acid is safe and provides sustained clinical benefits for men with metastatic CRPC. In secondary endpoints, zoledronic acid improves OS of ~ 2.7 months ($p=0.005$) (76).

More recently, a nuclear factor- β ligand (RANKL) inhibitor, denosumab, has been developed for the treatment of bone metastases. RANKL is involved in the regulation of bone metabolism and is overexpressed in osteoblasts associated with prostate cancer bone metastases in mice (77). Denosumab (120 mg subcutaneously q4 weeks) has been shown to significantly reduce and delay SREs similar to zoledronic acid in patients with bone metastases from breast cancer and other solid tumors (78,79). A phase III, randomized, non-inferiority trial (NCT00321620) in patients with bone metastases from CRPC is currently comparing the benefit of denosumab and zoledronic acid based on time to the first on-study SRE (80). More frequent adverse events were hypocalcemia (especially asymptomatic) in the denosumab arm (12.8 vs. 5.8% in the zoledronic arm), and acute phase reactions in the zoledronic arm (17.8 vs. 8.4% in the denosumab arm). The possible mechanisms of action of zoledronic acid, one of the most frequently employed bisphosphonates, and of denosumab in patients with bone metastases, are outlined in Fig. 1.

The authors reported a relatively low incidence of cumulative rate of the osteonecrosis of the jaw (ONJ) in patients receiving zoledronic acid (1.3%) and a similar incidence was observed in those receiving denosumab (2.3%; $p=0.09$) (81). Several studies found that ONJ usually occurs after a longer duration of zoledronic acid treatment (82,83) with a cumulative incidence of ONJ of $\sim 0.5\%$ at 1 year, 1.2% at 2 years and 1.4%

at 3 years (84). Therefore, considering that the average duration of this study is 12 month, it seems likely that the frequency of ONJ reported in the article is an underestimation of the actual ONJ frequency in both arms and that an additional and longer follow-up is necessary to draw final conclusions.

Another large, randomized, placebo-controlled trial was conducted to investigate the benefit of denosumab in patients receiving ADT, which can cause significant bone loss. Treatment with denosumab (60 mg q6 months) significantly increased bone mineral density of the lumbar spine at 24 months (+5.6% vs. -1%; $p<0.001$) and significantly reduced the incidence of new vertebral fractures (1.5 vs. 3.9%; $p=0.006$) compared with placebo (85,86).

4. Conclusions

The multidisciplinary management of advanced prostate cancer will no doubt continue to develop as chemotherapy and targeted agents are increasingly integrated into the treatment paradigm at all stages of disease to complement surgery, radiation, and hormonal therapies. Although the development of effective chemotherapy regimens for CRPC has led to significant improvements in OS, prognosis remains poor, and better treatment options are needed. At the present time, docetaxel represents the backbone of drug development strategies in CRPC, either as comparator in clinical trials or as the basis on which novel targeted agents are added. The natural history of CRPC is changing following the evidence that median OS has increased by 15 months after abiraterone and cabazitaxel treatment ($p<0.0001$). Together, these drugs should be considered an effective second-line treatment following docetaxel and are approved since 2010 by US FDA.

The increasing knowledge of the molecular pathways that contribute to prostate cancer growth, androgen independence and bone metastases should result in a better control of CRPC. The identification of biomarkers for patient selection is urgently needed in order to better tailor treatment according to the molecular phenotype of the tumor.

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