Overview of the latest treatments for castration-resistant prostate cancer

Mohamed Bishr and Fred Saad

Abstract | Over the past few years, we have developed an increased understanding of the molecular mechanisms that underlie prostate cancer progression and castration resistance and expanded our repertoire of therapeutic options for castration-resistant prostate cancer (CRPC). Four new agents (cabazitaxel, abiraterone acetate, enzalutamide, and radium-233) have been shown to prolong overall survival in patients with CRPC in the postchemotherapy setting. Targeting the androgen receptor pathway continues to have an important role in the treatment of CRPC, with abiraterone acetate and enzalutamide being the most exciting developments. Cabazitaxel is now considered the standard-of-care second-line chemotherapy for men with metastatic CRPC (mCRPC). Bone-targeted therapy is an active area of research, with denosumab being the first bone-targeted agent able to significantly delay the appearance of bone metastases in patients with CRPC and radium-223 being the first radiopharmaceutical agent to improve survival in patients with mCRPC.

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Introduction

As a result of our enhanced knowledge regarding the crucial role of the androgen receptor (AR) pathway in recurrent prostate cancer, the term 'castration-resistant prostate cancer' (CRPC) has replaced the formerly used terms 'androgen-independent prostate cancer' and 'hormone-refractory prostate cancer' for describing the clinical state at which prostate cancer progresses despite androgen deprivation therapy (ADT) and castrate levels of testosterone.[1] CRPC represents a spectrum of disease, ranging from asymptomatic nonmetastatic cancers (identified by rising PSA levels) to aggressive tumours with metastases that cause significant debilitation. Approximately 90% of patients with metastatic CRPC (mCRPC) have bone metastases, which can produce significant morbidity, including pain, pathologic fractures, spinal cord compression, and bone marrow failure.[2–4]

Based on our current understanding of the mechanisms underlying the development of CRPC, we can divide these mechanisms into two classes. The first class utilizes pathways involving the AR, such as AR amplification or mutation, generation of AR splice variants, deregulation of growth factors or cytokines, alteration of AR coactivators, and intratumoural (intracrine) production of androgen. The second class exploits pathways that bypass the AR, such as neuroendocrine differentiation of prostate cancer cells and deregulation of apoptotic genes.[5–14] In this Review, we present an overview of the different management approaches for patients with CRPC, paying particular attention to recently approved agents and therapies that have shown promising results in phase III trials (Figure 1).

Competing interests
F. Saad declares associations with the following companies: Astellas, Janssen, Sanofi, Amgen, Novartis, and Bayer. See the article online for full details of the relationships. M. Bishr declares no competing interests.

Targeting the AR pathway

Secondary hormonal manipulation

Given that AR signalling remains active in patients with CRPC, most guidelines recommend that ADT should be continued in these patients.[2] Secondary hormonal manipulation includes combined androgen blockade (CAB) by adding AR antagonists such as bicalutamide (for patients treated only by medical or surgical castration), discontinuation of AR antagonists for patients already on CAB to obtain an antiandrogen withdrawal response, replacement of one antagonist for another (such as nilutamide or flutamide), and the use of low-dose diethylstilbestrol (a synthetic ethinyl oestrogen) or ketoconazole (a nonspecific cytochrome P [CYP] inhibitor). For all these treatment approaches, transient PSA reductions have been reported in approximately 30% of patients, with no impact on overall survival.[15–19]

Systemic corticosteroid therapy

Corticosteroid therapy with low-dose prednisone or dexamethasone can produce symptomatic improvement and decreased PSA levels in more than one-third of patients with mCRPC. Suppression of adrenal androgen production is not the sole mechanism by which systemic corticosteroids exert their activity in men with CRPC; reduction of AR expression and the antiangiogenic effect mediated by the glucocorticoid receptor are also important mechanisms.[20–22] In addition, concomitant use of corticosteroids can help to reduce the adverse effects associated with chemotherapeutic agents and cytochrome P-17 (CYP17) inhibitors, such as abiraterone acetate.

Centre de Recherche (**M. Bishr**), Urology Division (**F. Saad**), Centre Hospitalier de l'Université de Montréal, 1560 Sherbrooke East, Montréal, QC H2L 4M1, Canada.

Correspondence to:
F. Saad
fred.saad@umontreal.ca

Key points

- The androgen receptor (AR) pathway remains a therapeutic target in patients with castration-resistant prostate cancer (CRPC)
- Abiraterone acetate, a selective *CYP17* inhibitor, has been approved by the FDA for the treatment of patients with metastatic CRPC (mCRPC) in prechemotherapy and postchemotherapy settings
- Enzalutamide (formerly known as MDV3100) is a multilevel AR inhibitor that has gained FDA approval for the treatment of patients with mCRPC who have already received docetaxel therapy
- Cabazitaxel, a taxane-based chemotherapeutic agent, is FDA-approved for patients who progress on, or after, docetaxel regimens
- Denosumab was the first osteoclast-targeted agent shown to significantly delay bone metastasis in patients with nonmetastatic CRPC
- Radium-223 was the first radiopharmaceutical agent shown to improve survival in patients with mCRPC

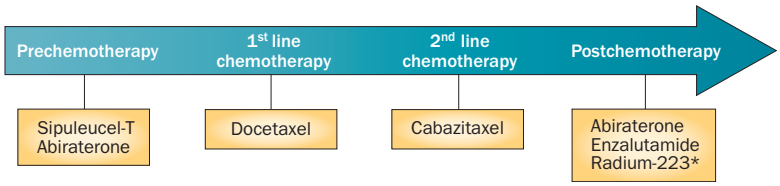

Figure 1 | Emerging therapies for metastatic castration-resistant prostate cancer. The arrow represents the course of the disease from diagnosis of mCRPC to death. Each box refers to the timing of each therapy throughout the course of the disease.

Abiraterone acetate

Abiraterone acetate is a highly selective irreversible inhibitor of CYP17, which is a critical enzyme for androgen biosynthesis in the adrenal gland and possibly also within prostate tumours.[23] In the multicentre phase III randomized trial COU-AA-301, abiraterone acetate plus prednisone prolonged median overall survival by 4.6 months compared with placebo plus prednisone (15.8 months versus 11.2 months; HR 0.74; $P = 0.0001$) for patients with mCRPC who had progressed after docetaxel treatment.[24] Moreover, all secondary end points indicated the superiority of abiraterone over placebo, including median time to PSA progression (8.5 months versus 6.6 months; HR 0.63; $P < 0.0001$), radiographic progression-free survival (PFS; 5.6 months versus 3.6 months; HR 0.66; $P < 0.0001$), confirmed PSA response rate (defined as ≥50% reduction in serum PSA from the pretreatment baseline; 29% versus 5.5%; $P < 0.0001$), and objective response as determined by Response Evaluation Criteria in Solid Tumours (RECIST; 14.8% versus 3.3%; $P < 0.0001$). As expected, adverse effects attributed to excess mineralocorticoid were more common in the abiraterone arm and were predominantly grade 1 or 2. In light of these positive results, abiraterone acetate was approved by the FDA, Health Canada and the European Medicines Agency (EMA) as second-line treatment for patients with CRPC.

In 2012, the phase III trial COU-AA-302—designed to evaluate the effects of abiraterone acetate plus prednisone versus placebo plus prednisone in patients with asymptomatic or mildly symptomatic mCRPC (without previous chemotherapy)—was unblinded after the second interim analysis of overall survival, which was performed after the observation of 333 deaths (43% of the required 773 events). More deaths were observed in the prednisone alone arm than in the abiraterone acetate plus prednisone arm (34% versus 27%) and the researchers recommended that patients in the placebo arm switch to abiraterone treatment. Men treated with abiraterone showed statistically significant improvements in radiographic PFS compared with placebo (16.5 months versus 8.3 months; HR 0.53; $P < 0.001$) and a mortality risk reduction of 25%. Median overall survival was not reached in the abiraterone arm but was 27.5 months in the placebo arm (HR 0.75; $P < 0.01$), indicating a strong trend towards increased overall survival. However, the prespecified P value for significance ($P \leq 0.001$) was not reached. In addition, all secondary end points, including time to opiate use for cancer-related pain, time to initiation of chemotherapy, time to decline in Eastern Cooperative Oncology Group performance score, and time to PSA progression, favoured the abiraterone arm.[25] Based on the results of this trial, the FDA and the EMA approved the use of abiraterone acetate with prednisone for treating chemotherapy-naive mCRPC in 2012.

Enzalutamide

Enzalutamide (formerly MDV3100) is a potent multilevel competitive inhibitor of the AR, binding to the AR with higher affinity than bicalutamide and preventing nuclear translocation and DNA binding. The latter two mechanisms are unique to enzalutamide. In contrast to other AR antagonists, enzalutamide has no agonistic activity. It also induces shrinkage of LNCaP xenograft tumours, whereas other conventional AR antagonists can only retard growth.[26] Enzalutamide was approved by the FDA in 2012 based on the results of the AFFIRM study, which compared the effects of enzalutamide with placebo in patients previously treated with docetaxel. Enzalutamide demonstrated a significant advantage over placebo in median overall survival of 4.8 months (18.4 months versus 13.6 months; HR 0.62; $P < 0.0001$) and all secondary end points, including confirmed PSA response rate (54% versus 2%; $P < 0.001$), soft-tissue response rate (29% versus 4%, $P < 0.001$), time to PSA progression (8.3 months versus 3.0 months; HR 0.25; $P < 0.001$), radiographic PFS (8.3 months versus 2.9 months; HR 0.40; $P < 0.001$), and time to first skeletal-related event (SRE; 16.7 months versus 13.3 months; HR 0.69; $P < 0.001$). The most common adverse events reported in the enzalutamide group were fatigue, diarrhoea, and hot flashes. Seizures were reported in 0.6% of patients receiving enzalutamide, several of whom had predisposing conditions or were taking concomitant medications that are known to lower the seizure threshold. On the basis of these results, an independent data and safety monitoring committee recommended that the study be halted and unblinded, with eligible patients in the placebo group offered treatment with enzalutamide.[27] The PREVAIL trial, which was set up to evaluate the benefit of enzalutamide therapy in the prechemotherapy setting, is ongoing (Table 1).[28]

Immunotherapy

Sipuleucel-T

Sipuleucel-T is a therapeutic cancer vaccine.[29] It is considered to be an active cellular immunotherapy, using

Table 1 | Therapeutic agents in phase III trials for the treatment of CRPC

Clinical trial	Therapeutic agents	Type of agent
Prechemotherapy		
NCT01322490[34]	PROSTVAC-V/F (with or without GM-CSF) vs placebo	Immunotherapy
NCT01212991[28]	MDV3100 vs placebo	AR-pathway-targeting agent
NCT01057810[39]	Ipilimumab vs placebo	Immunotherapy
NCT01193244[76]	Orteronel (with prednisone) vs placebo (with prednisone)	AR-pathway-targeting agent
NCT01234311[82]	Tasquinimod vs placebo	Angiogenesis-targeting agent
First-line chemotherapy		
NCT01308567[48]	Cabazitaxel (with prednisone) vs docetaxel (with prednisone)	Cytotoxic chemotherapy
Adjunct to first-line chemotherapy		
NCT00744497[78]	Dasatinib (with docetaxel plus prednisone) vs placebo (with docetaxel plus prednisone)	Bone-targeting agent
NCT01188187[79]	Custirsen (with docetaxel plus prednisone) vs docetaxel or prednisone alone	Nonhormonal intracellular-pathway-targeting agent
Second-line chemotherapy		
NCT01308580[47]	Cabazitaxel (20 mg/m^2 vs 25 mg/m^2) with prednisone	Cytotoxic chemotherapy
Adjunct to second-line chemotherapy		
NCT01578655[81]	Custirsen (with cabazitaxel plus prednisone) vs cabazitaxel plus prednisone alone	Nonhormonal intracellular-pathway-targeting agent
NCT01083615[80]	Custirsen (with docetaxel or cabazitaxel plus prednisone) vs placebo (with docetaxel or cabazitaxel plus prednisone)	Non-hormonal intracellular pathway targeting agent
Postchemotherapy		
NCT01193257[77]	Orteronel (with prednisone) vs placebo (with prednisone)	AR-pathway-targeting agent
NCT00861614[40]	Ipilimumab vs placebo (following radiotherapy)	Immunotherapy
NCT01605227[83]	Cabozantinib vs prednisone	Non-hormonal intracellular pathway targeting agent
NCT01522443[84]	Cabozantinib vs mitoxantrone or prednisone	Non-hormonal intracellular pathway targeting agent

Abbreviations: AR, androgen receptor; CRPC, castration-resistant prostate cancer; GM-CSF, granulocyte-macrophage colony-stimulating factor.

autologous antigen-presenting cells loaded *ex vivo* with a recombinant fusion protein called PA2024 that consists of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor (GM-CSF).[30] In 2010, sipuleucel-T became the first immunotherapeutic agent to be approved by the FDA for prostate cancer, based on the results of the double-blind, placebo-controlled, multicentre IMPACT trial. This study, which involved 512 men with mCRPC, showed a 22% relative reduction in the risk of death in the sipuleucel-T arm compared with the placebo arm (overall survival of 25.8 months versus 21.7 months; HR 0.78; $P = 0.03$). The treatment was well tolerated; the most common complications included mild or moderate chills, pyrexia, and headaches, all of which were transient. In contrast to overall survival, there was no significant difference between the study groups in terms of PSA response or PFS.[31] However, given the cost and our limited ability to predict who will actually benefit from sipuleucel-T, the drug has not gained widespread adoption outside the USA.

Other immunotherapeutic agents

PROSTVAC-V/F is a poxviral-based PSA-targeted vaccine that showed promising results in phase II trials.[32,33] In a double-blinded randomized controlled phase II study, PROSTVAC-V/F immunotherapy was well tolerated and associated with a 44% reduction in mortality rate and an 8.5 month improvement in median overall survival (25.1 months versus 16.6 months; HR 0.56; $P = 0.006$) in men with mCRPC compared with controls. However, it is worth mentioning that this trial was not powered to detect an overall survival difference and that the primary end point for this trial was PFS, which was similar in the two groups ($P = 0.6$).[33] Currently, an ongoing phase III study is evaluating overall survival for men receiving either PROSTVAC-V/F plus adjuvant dose GM-CSF, PROSTVAC-V/F without GM-CSF, or placebo (Table 1).[34]

Ipilimumab is a human monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), which is a negative regulator of T-cell activation.[35] Preliminary results from phase I/II trials showed that ipilimumab alone or in combination with GM-CSF or radiotherapy can enhance the efficiency of the anti-tumour immune response.[36–38] Phase III studies to evaluate ipilimumab in prechemotherapy and postchemotherapy setting are ongoing (Table 1).[39,40]

Systemic chemotherapy

First-line regimens

Since 2004, docetaxel (a taxane that induces polymerization of microtubules and phosphorylation of bcl-2

protein) has replaced mitoxantrone as the first-line standard-of-care treatment for patients with detectable mCRPC, based largely on the results of the two pivotal trials TAX327 and SWOG 9916. In the TAX327 trial, 1,006 patients with mCRPC were randomly assigned to receive either docetaxel (75 mg/m^2 every 3 weeks or 30 mg/m^2 every week) plus prednisone or mitoxantrone (12 mg/m^2 every 3 weeks) plus prednisone. Men who received docetaxel (75 mg/m^2 every 3 weeks) plus prednisone demonstrated a statistically significant improvement in overall survival of 2.4 months compared with mitoxantrone plus prednisone (18.9 months versus 16.5 months; HR 0.76; $P = 0.009$). When compared with the mitoxantrone-plus-prednisone treatment arm, significantly more patients treated with docetaxel (75 mg/m^2 every 3 weeks) plus prednisone achieved ≥50% reductions in serum PSA (45% versus 32%; $P < 0.001$), pain response (35% versus 22%; $P = 0.01$) and quality of life (QOL) response (22% versus 13%; $P = 0.009$). Although neutropenia was more common in the group given docetaxel (75 mg/m^2 every 3 weeks) and prednisone, febrile neutropenia and serious infections were rare.[4] Similarly, in the SWOG 9916 trial, a combination of docetaxel and estramustine prolonged median overall survival by 1.9 months (17.5 months versus 15.6 months; HR 0.80; $P = 0.02$) and PFS by 3.1 months (6.3 months versus 3.2 months; HR 0.73; $P < 0.0001$) compared with mitoxantrone plus prednisone.[3]

Second-line regimens

Until a few years ago, no life-prolonging second-line treatment options were available for patients with tumours in the docetaxel-resistant or postdocetaxel state. Mitoxantrone was considered to be the *de facto* second-line chemotherapy despite its limited activity and increased toxicity in that setting, with response rates ranging from 9–20% in retrospective series.[41–43] All this changed in 2010 when the FDA approved cabazitaxel as a new option for patients with mCRPC previously treated with docetaxel. In 2011, cabazitaxel was also approved by the EMA and Health Canada. Cabazitaxel is a potent taxane agent that, unlike other taxanes, has low affinity for P-glycoprotein, an adenosine-triphosphate-dependent drug efflux pump that is overexpressed in taxane-resistant tumour cells.[44]

The approval of cabazitaxel was based primarily on data from the TROPIC study, which showed statistically significant and clinically relevant improvements in median overall survival (15.1 months versus 12.7 months; HR 0.70; $P < 0.0001$), PFS (2.8 months versus 1.4 months; HR 0.74; $P < 0.0001$), and PSA response rate (39.2% versus 17.8%; $P = 0.0002$) in men treated with cabazitaxel plus prednisone compared with mitoxantrone plus prednisone. Cabazitaxel was associated with increased rates of clinically significant grade 3 or 4 adverse effects compared with mitoxantrone, including neutropenia (82% versus 58%), febrile neutropenia (8% versus 1%), and diarrhoea (6% versus <1%). The incidence of these adverse effects was affected by age and previous radiotherapy. Moreover, cabazitaxel was associated with a higher incidence of treatment-related mortality than mitoxantrone (5% versus 2%).[45] Patient education, acute specialized care access, dose modifications (including delays and reductions), and initial prophylaxis with GM-CSF are all potential strategies for mitigating the risks of adverse events or treatment-related mortality, especially for patients aged >65 years, patients with presence of visceral metastases, or patients with compromised bone marrow reserve.[46]

With the aim of minimizing the toxicities observed in patients receiving 25 mg/m^2 cabazitaxel in the TROPIC study, the phase III study PROSELICA[47] has been set up to evaluate whether 20 mg/m^2 cabazitaxel is noninferior to 25 mg/m^2 cabazitaxel (both administered in combination with prednisone) in terms of overall survival in patients with postdocetaxel mCRPC. Another phase III study, FIRSTANA, was designed to determine the efficacy of cabazitaxel as a first-line chemotherapy and is now recruiting patients.[48] The aim of this trial is to demonstrate the superiority of cabazitaxel (25 mg/m^2 or 20 mg/m^2) plus prednisone over docetaxel (75 mg/m^2) plus prednisone in terms of overall survival in patients with mCRPC who have not been previously treated with chemotherapy (Table 1).

For patients who have not demonstrated definitive evidence of resistance to docetaxel, retreatment with docetaxel remains an option.[49–53] In a prospective phase II study, 24.5% of men with mCRPC treated with docetaxel rechallenge responded with a reduction in PSA level of ≥50%, median PFS of 5 months, and median overall survival of 13 months.[51] An initial promising response to first-line docetaxel treatment (in terms of reduction in PSA level ≥50% and time interval to progression of >3 months) was associated with an increased efficacy of subsequent docetaxel reintroduction.[52,53]

Bone-targeting therapy

Patients with prostate cancer are vulnerable to bone loss and at significant risk of skeletal complications, such as pathologic fractures, debilitating bone pain, and spinal cord compression. Bone fragility can be attributed to the cancer itself, which is a risk factor for osteoporosis, ADT-associated bone loss, and bone metastases.[54,55] More than 90% of men with prostate cancer have inadequate calcium intake (<1 g/day);[56] thus, calcium and vitamin D supplementation and calcium-level monitoring are important for the prevention of hypocalcaemia.

Bisphosphonates

Bisphosphonates were the first, and are now the most widely used, bone-targeted agents. Owing to their structural similarity to pyrophosphate, a normal component of bone matrix, they bind to hydroxyapatite crystals and are integrated into the bone matrix, resulting in the inhibition of osteoclast-mediated bone resorption. Multiple RCTs have shown that bisphosphonates significantly reduce ADT-related bone loss in men with nonmetastatic prostate cancer.[57–62] However, none of these trials were sufficiently powered to demonstrate a reduction in the risk of fractures.

In patients with mCRPC, zoledronic acid is the only bisphosphonate (and the first osteoclast-targeted agent) to show a protective effect against SREs. In a randomized controlled phase III study, zoledronic acid at 4 mg every 3 weeks resulted in a 48% reduction in the mean annual incidence of SREs ($P = 0.005$), a 5-month prolongation of the median time to first SRE ($P = 0.009$), and a 36% reduction in the risk of SRE.[63,64] In 2002, results of this trial led to FDA and EMA approval of zoledronic acid for the prevention of SREs in patients with mCRPC.

Bisphosphonate-induced nephrotoxicity raises some concerns, especially when administered intravenously. Thus, monitoring of serum creatinine before each dose, dose adjustment according to creatinine clearance, and avoiding rapid infusion (infusion should not take <15 min) are crucial for reducing the risk of impaired renal function. Other potential effects include self-limiting bone pain and flu-like symptoms, typically occurring after the first infusion. Hypocalcaemia and osteonecrosis of the jaw (ONJ) are other adverse effects that require attention.[65]

Denosumab

Denosumab is a human monoclonal antibody that specifically targets the osteoblast-secreted receptor activator of nuclear factor KB ligand (RANKL) and prevents it from binding to its receptor (RANK) on the surface of osteoclast cells, leading to inhibition of bone loss.[66] In patients with nonmetastatic prostate cancer who are receiving ADT, denosumab (60 mg given subcutaneously every 6 months) was the first bone-targeted agent to demonstrate both an improvement in bone mass density at all sites (lumbar spine, total hip, femoral neck, and distal third of the radius) at all analysed time points and a reduction in the incidence of new vertebral fractures (1.5% versus 3.9%; $P = 0.006$) when compared with placebo.[67]

In an RCT of men with mCRPC, denosumab (120 mg given subcutaneously every 4 weeks) was shown to be superior to zoledronic acid (4 mg given intravenously every 3 weeks) in terms of delaying the time to first SRE (20.7 months versus 17.1 months; $P < 0.001$ for non-inferiority; $P = 0.008$ for superiority). No difference in overall survival or PFS was seen between the two agents.[68] Hypocalcaemia was expected in both groups (owing to the mechanism of action of antiresorptive agents) and was seen more frequently with denosumab than with zoledronic acid (13% versus 6%; $P < 0.0001$); thus, it is important to appropriately replete vitamin D levels before the initiation of therapy and to monitor calcium levels while on therapy. Denosumab has not been reported to cause nephrotoxicity and is thought to be safe regardless of renal function.[69] In 2012, denosumab was shown to be the first bone-targeted agent able to significantly delay bone metastasis in patients with nonmetastatic CRPC by 4.2 months compared with placebo (29.5 months versus 25.2 months; HR 0.85; $P = 0.028$). A significant delay in symptomatic bone metastasis was also noted. No difference in overall survival was found between denosumab and placebo groups in this study.[70] At the present time, denosumab has not received FDA approval for use in the prevention of bone metastases.

Another concern related to osteoclast-targeted therapy (especially with potent agents like zoledronic acid and denosumab) is ONJ, which is defined as exposed necrotic bone in the maxillofacial region that persists for more than 8 weeks. In one study, the risk of ONJ in patients receiving denosumab was 4.6%.[70] No significant difference was observed in the incidence of ONJ in patients with mCRPC who received denosumab compared with zoledronic acid (2.3% versus 1.3%; $P = 0.09$).[68] Although the aetiology of ONJ is unclear, duration of therapy, previous dental pathology, dental surgery or dentures, concomitant corticosteroid use, radiotherapy, and chemotherapy are all identified risk factors. Excellent oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce the risk.[71]

Radiopharmaceuticals

Systemic radiopharmaceuticals are bone-seeking agents that emit radiation or are linked to a radioactive emitter, enabling the preferential delivery of radiation to areas of high bone turnover. The β-emitting pharmaceuticals strontium-89 and samarium-153 are FDA-approved for the palliation of pain caused by bone metastases and are particularly indicated in patients with multifocal bone metastases.[72] The major concern when using these agents is myelosuppression caused by β-particle penetration to adjacent bone marrow.

In the phase III trial ALSYMPCA, treatment with radium-223 (an α-emitting agent) resulted in an improvement in median overall survival of 3.6 months (14.9 months versus 11.3 months; HR 0.695; $P = 0.00007$) in patients with symptomatic mCRPC (≥2 bone metastases and no visceral metastases) when compared with placebo. This study also demonstrated significant improvement in time to first SRE (15.6 months versus 9.8 months; HR 0.658; $P = 0.00037$) and in QOL response rate (27% versus 18%; $P < 0.05$) in the radium-223 group compared with the placebo group. In this study population, 58% of patients had received prior docetaxel treatment. Overall, radium-223 was well tolerated, with only a slight increase reported in the incidence of myelosuppression compared with placebo. Rates of grade 3 or 4 neutropenia and thrombocytopenia were 2.2% and 6.3%, respectively, for men who received treatment compared with 0.7% and 2%, respectively, in placebo controls.[73,74]

Conclusions

Over the past decade, the therapeutic options available for men with mCRPC have increased markedly.[75] Hormone-related therapies, such as abiraterone and enzalutamide, can significantly prolong overall survival in patients with mCRPC and are very well tolerated. Other potent agents that target the AR pathway, such as orteronel, are under evaluation in phase III trials.[76,77] Sipuleucel-T is the first immunotherapeutic agent to be effective against prostate cancer and other

immunotherapeutic agents—such as ipilimumab (a CTLA4 inhibitor) and PROSTVAC (a poxvirus-based PSA-targeted immunotherapy)—are currently under investigation. Docetaxel-based chemotherapy remains a cornerstone in the treatment of mCRPC and cabazitaxel has become the standard second-line chemotherapy. Clinical trials of new agents that can be combined with both of these chemotherapies (in an attempt to further enhance their efficacy) are ongoing.[78–81]

Osteoclast-targeted agents, such as denosumab and zoledronic acid, significantly reduce the risk of SREs in patients with mCRPC. Denosumab was the first bone-targeted agent to show a significant reduction in the incidence of new vertebral fractures in patients with nonmetastatic hormone-sensitive prostate cancer and it was also the first bone-targeted agent to significantly delay bone metastasis in patients with nonmetastatic CRPC. With all these effective therapeutic options and continued research, there is renewed optimism for patients with castration-resistant disease. The challenge for the future will be to establish a rational and evidence-based approach for using these agents to optimize outcomes and minimize costs.

Review criteria

We reviewed the relevant medical literature published until March 2013 for full-length English-language articles and abstracts, with a particular emphasis on new agents with positive phase III results for patients with metastatic castration-resistant prostate cancer. PubMed search terms included "castration-resistant prostate cancer", "hormone-resistant prostate cancer", "androgen receptor", "abiraterone acetate", "MDV", "sipuleucel-T", "docetaxel", "cabazitaxel", "zoledronic acid", "denosumab", and "radium-223". Reference lists of included articles were reviewed for relevant trials.

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Author contributions

M. Bishr researched the literature for this Review. Both authors wrote, edited, discussed, and reviewed the manuscript prior to submission.