Recent developments in treatments targeting castration-resistant prostate cancer bone metastases

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Received 22 July 2011; revised 30 September 2011; accepted 5 October 2011

Background: Prostate cancer is the most common male cancer and one of the top causes of male cancer-related death. Most patients with prostate cancer respond to initial androgen deprivation therapy before progressing to castration-resistant prostate cancer (CRPC) and eventually developing bone metastases. Growth of prostate cancer metastases in the bone microenvironment produces numerous factors that disrupt the dynamic equilibrium of osteogenesis and osteolysis existing in healthy bone, leading to progressive morbidity, poor quality of life, and increased treatment costs.

Materials and methods: Relevant studies of CRPC and targeted therapies were identified from literature and clinical trial databases, websites, and conference abstracts.

Results: Available data on agents potentially targeting bone metastatic CRPC or the bone microenvironment in patients with CRPC are discussed, including inhibitors of tumor growth/survival and bone turnover (SRC family kinase inhibitors, endothelin-1 inhibitors, MET inhibitors, and thalidomide and its derivatives), inhibitors of bone turnover (bisphosphonates and receptor activator of nuclear factor-κB ligand inhibitors), antiangiogenic agents (vascular endothelial growth factor receptor and platelet-derived growth factor blockers), prostate cancer vaccines, and bone-directed radiopharmaceuticals.

Conclusions: With increasing data availability demonstrating tumor–bone microenvironment interactions and routine incorporation of bone-related end points into CRPC trials, bone microenvironment-targeted agents are likely to become an increasingly important component of CRPC treatment.

Key words: bisphosphonates, immunotherapy, growth factors, RANKL, SRC

Introduction

Prostate cancer is the most common male cancer in the United States and Europe and one of the top three causes of male cancer-related death [1, 2]. Although most patients with advanced metastatic disease initially respond to androgen deprivation therapy (ADT), experiencing disease control for a median of 13–22 months [3], the majority of patients eventually progress and are considered to have castration-resistant prostate cancer (CRPC) [4]. CRPC progression is associated with increased incidence of metastases that are predominantly detectable in bone; however, visceral (lung and liver) metastases can also occur [5].

Prostate cancer bone metastases produce a variety of factors that disturb the osteoblast–osteoclast equilibrium (bone formation/lysis equilibrium) seen in healthy bone [5]. In CRPC, osteoblast-mediated bone formation eventually surpasses increased osteoclastic resorption, ultimately forming woven bone composed of disorganized collagen bundles, which has suboptimal strength [6]. Structurally compromised bone combined with underlying osteolysis increases incidences of skeletal-related events (SREs), including pain, predisposition to fractures, and spinal cord compression, causing impaired mobility, loss of functional independence, and necessitating surgery and/or radiotherapy to treat bone lesions [7, 8]. Structural effects of CRPC bone metastases are therefore associated with substantial and progressive morbidity, diminishing quality of life (QoL), and increasing treatment costs [7–10]. Patients with CRPC often consider bone pain their most debilitating symptom, leading to substantially reduced QoL.

Until recently, first- and second-line treatment options for patients with CRPC were limited. Recommended first-line treatment for metastatic CRPC is systemic docetaxel-based chemotherapy [11], which provides a median survival <20 months and median time to progression (TTP) of 6 months [12, 13]. Sipuleucel-T, an autologous cellular immunotherapy, was approved in 2010 by the Food and Drug Administration (FDA) for treating asymptomatic or minimally symptomatic metastatic CRPC. Cabazitaxel, a microtubule-targeting drug,
and abiraterone acetate, a CYP17 inhibitor (androgen biosynthesis pathway), were recently approved in the United States for progressive metastatic CRPC following prior docetaxel-based chemotherapy [14, 15]. Various therapies in development for CRPC are shown in Table 1.

Because CRPC has a propensity for metastasizing to bone, effective treatments targeting both the tumor and resulting metastatic lesions or the bone microenvironment are needed [16]. We discussed the development of therapeutic agents targeting CRPC bone metastases.

**the bone metastatic microenvironment**

Metastatic bone lesion pathogenesis is a complex interaction between bone stromal cells (osteoclasts and osteoblasts), endothelial cells, immunologic cells, and tumor cells. Metastatic prostate cancer cells that have migrated to the bone marrow cavity extravasate, invade the marrow stroma, and travel to the bone surface where they stimulate osteoclast and osteoblast formation and activity, causing a net increase in bone remodeling [6, 17]. This process is facilitated by tumor-derived factors including parathyroid hormone-related peptide, which activates stromal cells to produce receptor activator of nuclear factor-κB ligand (RANKL), stimulating osteoclast differentiation/activity along with other factors including bone morphogenetic protein, transforming growth factor-β, fibroblast growth factor, vascular endothelial growth factor (VEGF), MDA-BF-1, and Wnt. In addition to tumor-derived factors, osteoblast/osteoclast-derived factors including epidermal growth factor, endothelin-1 (ET-1), tumor necrosis factor-α, and interleukin-1α add to the complex signaling network regulating the bone metastatic microenvironment (Figure 1) [19, 20]. Bone resorption also releases growth factors from the bone matrix that can enhance proliferation and differentiation of osteoblasts and promote tumor cell proliferation. Tumor/stroma-derived VEGF and ET-1 appear to be critical in supporting and sustaining tumor colonization of bone [21–24].

**agents with combined antitumor and antiosteoclast effects**

Several agents have been developed that could simultaneously decrease tumor growth, prevent metastases, and inhibit tumor-associated bone pathology of metastatic prostate cancer [16].

**bisphosphonates**

Bisphosphonates are inorganic pyrophosphate derivatives that are preferentially incorporated into bone matrix at sites of active bone remodeling that promote osteoclast apoptosis [25, 26]. By reducing osteolytic activity, bisphosphonates also inhibit tumor proliferation by depriving tumor of bone-derived growth factors released during osteolysis [27]. Zoledronic acid is an established bisphosphonate treatment of managing bone metastatic CRPC following progression on ADT. In placebo-controlled studies, zoledronic acid significantly reduced incidence and delayed onset of SREs [11, 28–30]. Despite proven efficacy against SREs, zoledronic acid did not significantly improve overall survival (OS) compared with placebo [28]. Zoledronic acid use is associated with hypocalcaemia if administered in combination with loop diuretics and osteonecrosis of the jaw (ONJ) has been reported [31].

Preclinical evidence suggests that bisphosphonates may directly inhibit prostate tumor cells [32]. In vitro, bisphosphonates induce cell death and/or cytostasis in prostate cancer cell lines and inhibit tumor cell adhesion, migration, and invasion [33–35]. Antitumor activity has also been seen in mouse models of prostate cancer, including prostate tumor growth inhibition in situ and in bone, and decreased metastasis to prostate-draining lymph nodes [36, 37]. Combining bisphosphonates with cytotoxic agents such as taxanes may result in synergistic antitumor activity [38–42]. Adding zoledronic acid to a docetaxel regimen significantly inhibited prostate tumor growth in mouse tibiae compared with docetaxel alone [43].

Investigations are ongoing to determine whether preclinical antitumor activity of bisphosphonates translates into any clinical effect for patients with CRPC [44].

Bisphosphonate activity in patients with CRPC is being evaluated in the RADAR (Randomised Androgen Deprivation and Radiotherapy, NCT00195856), ZEUS (Zometa EUropean Study, NTR355), and STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy, NCT00268476) clinical trials.

**ET receptor inhibitors**

ET-1, a potent vasoconstrictor peptide, is produced by a variety of normal cells, including endothelial cells and epithelial tissues, and is mitogenic for many cell types, including osteoblasts [45]. In vitro, ET-1 induces proliferation of human prostate cancer cell lines and potently stimulates osteoblast proliferation and new bone formation by mouse calvaria explants [46, 47]. Elevated plasma ET-1 levels have been detected in patients with prostate cancer, and increased ET-1 immunoreactivity has been detected in specimens from patients with advanced prostate cancer [46]. These findings, combined with ET-1’s role in the osteoblastic response, led to ET receptor inhibitors atrasentan and zibotentan being developed [48].

In a mouse prostate cancer metastasis model, single-agent atrasentan specifically inhibited prostate cancer growth in bone but not in soft tissues [49]. Combining paclitaxel or docetaxel with atrasentan had additive proapoptotic effects in prostate cancer cells, and combining docetaxel and atrasentan significantly reduced tumor xenograft growth [50]. A second study showed that atrasentan combined with docetaxel blocked prostate tumor growth within the bone environment more effectively than either agent alone [51]. Zibotentan has also shown preclinical antitumor activity. In vitro, zibotentan induced prostate cancer cell apoptosis, and cytotoxicity was increased by adding paclitaxel, docetaxel, or doxorubicin [52].

Atrasentan and zibotentan have been evaluated in patients with CRPC [53]. In a randomized phase II trial, atrasentan monotherapy prolonged TTP and significantly delayed prostate-specific antigen (PSA) progression compared with
Table 1. Agents under clinical investigation for metastatic castration-resistant prostate cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Drug class</th>
</tr>
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<tbody>
<tr>
<td>Abarelix</td>
<td>LHRH receptor antagonist, testosterone antagonist</td>
<td>Oligopeptide</td>
</tr>
<tr>
<td>Afibertcept</td>
<td>Angiogenesis inhibitor, placenta growth factor inhibitor, VEGF A inhibitor</td>
<td>Recombinant fusion protein</td>
</tr>
<tr>
<td>Atrasentan</td>
<td>Endothelin A receptor antagonist</td>
<td>Pyrrolidine</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF A inhibitor</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>Testosterone congener inhibitor</td>
<td>Anilide, nitrile, small molecule, tosyl compound</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Tubulin polymerization promoter</td>
<td>Taxane</td>
</tr>
<tr>
<td>Cilengitide</td>
<td>Integrin alpha_vbeta, and alpha_vbeta, antagonist</td>
<td>Cyclic peptide</td>
</tr>
<tr>
<td>Custirsen</td>
<td>Clustering inhibitor</td>
<td>Antisense oligonucleotide, thionucleotide</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>SRC family kinase, BCR-ABL, EphA2 receptor, PDGF beta receptor, and c-KIT inhibitor</td>
<td>Pyrimidine, small molecule, thiazole</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL inhibitor</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Mitosis inhibitors, tubulin modulators, tubulin polymerization promoters</td>
<td>Small molecule, taxane</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>DNA synthesis inhibitors</td>
<td>Deoxyribonucleoside, pyrimidine nucleoside, small molecule</td>
</tr>
<tr>
<td>Histrelin acetate</td>
<td>Gonadotropin-releasing hormone stimulant</td>
<td>Pituitary hormone-releasing hormone</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA4 inhibitor, immunostimulant, T lymphocyte stimulant</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Cell cycle inhibitors, tubulin polymerization promoters</td>
<td>Epothilone, macrolide, small molecule</td>
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<tr>
<td>Lenalidomide</td>
<td>Angiogenesis inhibitor, immunomodulator, interleukin-1beta inhibitor, interleukin-10 inhibitor, TNF inhibitor</td>
<td></td>
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<tr>
<td>Leuprorelin</td>
<td>Gonadotropin-releasing hormone stimulant</td>
<td>Gonadotropin, oligopeptide, pituitary hormone-releasing hormone</td>
</tr>
<tr>
<td>MDV 3100</td>
<td>Androgen receptor antagonist</td>
<td>Small molecule, small molecule</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>DNA inhibitors, DNA topoisomerase inhibitors, Immunosuppressants, type II DNA topoisomerase inhibitor</td>
<td></td>
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<tr>
<td>MLN 8237</td>
<td>Aurora kinase A inhibitor</td>
<td>Benzazepine, benzoic acid, pyrimidine, small molecule</td>
</tr>
<tr>
<td>Nilutamide</td>
<td>Testosterone congener inhibitor</td>
<td>Imidazolidine, nitrobenzene, small molecule</td>
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<tr>
<td>OGX 427</td>
<td>HSP27 heat shock protein inhibitor</td>
<td>Antisense oligonucleotide</td>
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<tr>
<td>Picoplatin</td>
<td>DNA cross-linking agents, DNA synthesis inhibitor</td>
<td>Platinum complex, small molecule</td>
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<tr>
<td>Prostate cancer vaccines</td>
<td>Immunostimulant</td>
<td>Cancer vaccine</td>
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<td>Radium 223</td>
<td>Ionizing agent</td>
<td>Radiopharmaceutical</td>
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<tr>
<td>Sagopilone</td>
<td>Mitosis inhibitors, tubulin modulators, tubulin polymerization promoter</td>
<td>Epothilone</td>
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<tr>
<td>Samarium 153 leudronam</td>
<td>Ionizing agents, reactive oxygen species stimulant</td>
<td>Analgesic, inorganic chemical, radiopharmaceutical</td>
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<tr>
<td>Saracatinib</td>
<td>SRC family kinase inhibitor</td>
<td>Benzoindioxide, quinazoline, small molecule</td>
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<tr>
<td>Satraplatin</td>
<td>DNA cross-linking agent, DNA synthesis inhibitor</td>
<td>Cyclohexylamine, platinum complex</td>
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<tr>
<td>SB 939</td>
<td>Histone deacetylase inhibitor</td>
<td>Acrylamide, hydroxamic acid, small molecule</td>
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<tr>
<td>Sipuleucel-T</td>
<td>Immunostimulants, T lymphocyte stimulant</td>
<td>Cancer vaccine, cell therapy, dendritic cell vaccine, tissue extract</td>
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<tr>
<td>Sorafenib</td>
<td>Angiogenesis inhibitor, kinase inhibitor of FMS-like tyrosine kinase 3, MAPK, PDGFR beta, c-RET, c-KIT, RAF kinase, VEGFR2/3</td>
<td>Benzenesulfonate, pyridine, small molecule</td>
</tr>
<tr>
<td>Strontium 89</td>
<td>Ionizing agent</td>
<td>Radiopharmaceutical</td>
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<tr>
<td>Sunitinib</td>
<td>Angiogenesis inhibitor, kinase inhibitor of CSF receptor, FMS-like tyrosine kinase 3, PDGFR beta, c-RET, c-KIT, and VEGFR1–3</td>
<td>Indole, pyrrole, small molecule</td>
</tr>
<tr>
<td>TAK-700</td>
<td>Steroid 17-alpha-hydroxylase inhibitor</td>
<td>Two-ring heterocyclic compound, amide, naphthalene, small molecules</td>
</tr>
<tr>
<td>TH 302</td>
<td>Alkylation agent</td>
<td>Nitroimidazole, small molecule</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Angiogenesis inhibitor, immunosuppressant, TNF inhibitor</td>
<td>Phthalimide, piperidine</td>
</tr>
<tr>
<td>Tigapolitide</td>
<td>Angiogenesis inhibitor, apoptosis stimulant, MMP inhibitor, signal transduction pathway inhibitor</td>
<td></td>
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<tr>
<td>Veliparib</td>
<td>Poly(ADP-ribose) polymerase inhibitor</td>
<td>Benzimidazole</td>
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<td>Bone resorption factor inhibitor, HMG-CoA reductase inhibitor, osteoclast inhibitor</td>
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CSF, colony-stimulating factor; CTLA4, cytotoxic T lymphocyte antigen 4; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; LHRH, lutenizing hormone-releasing hormone; MAPK, mitogen-activated protein kinase; MMP, matrix metalloprotease; PDGFR, platelet-derived growth factor receptor; RANKL, receptor activator of nuclear factor kappa-B ligand; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Figure 1. Interaction between metastatic prostate cancer cells and the bone microenvironment. BMP, bone morphogenic protein; ET-1, endothelin 1; FGF, fibroblast growth factor; IL-1α, interleukin-1 α; IL-6, interleukin-6; OB, osteoblast; OC, osteoclast; Obp, osteoblastic progenitor cells; Ogp, osteoclastic progenitor cells; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PSA, prostate-specific antigen; PTHrP, parathyroid hormone-related protein; RANKL, receptor activator of NF-κB ligand; S, stromal cell; SDF, stromal-derived factor; TFα, Thomas Friedrich antigen; TGFB, transforming growth factor-β; TNFα, tumor necrosis factor-α; uPA, urokinase plasminogen activator; VEGF, vascular endothelial growth factor. Reproduced from Loberg et al. 2005 [18].

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placemen [54]. However, in phase III trials of metastatic or nonmetastatic CRPC, atrasentan did not reduce disease progression or delay TTP relative to placebo despite effects on PSA [55, 56]. In a phase II/III study of atrasentan combined with docetaxel in metastatic CRPC, 23% of patients had a confirmed PSA response and significant declines in bone alkaline phosphatase (BAP); a bone formation marker; and serum N-telopeptide (NTX); a bone resorption marker were observed [57]. In a phase I dose-escalation study of zibotentan in metastatic CRPC, no PSA responses occurred, although prolonged stable disease (SD) was reported including one patient who maintained stable PSA for 20 months [58]. The multicenter phase II trial of zibotentan in men with CRPC and bone metastases who were pain free or mildly symptomatic for pain found improved OS for zibotentan treatment groups compared with placebo but no significant difference in TTP. Bone-related end points from this study are yet to be reported [59]. A randomized phase III trial in men with stage IV CRPC and bone metastases (NCT00134056) compared the docetaxel, prednisone, and atrasentan combination with docetaxel plus prednisone. However, the study was closed early at the request of the data monitoring committee (DMC) after a planned interim analysis found that the atrasentan combination provided no benefit [60].

Phase III trials in CRPC are currently assessing docetaxel with or without zibotentan (ENTHUSE M1C; NCT00617669). However, recent results from the ENTHUSE M1 trial (NCT00554229) showed no significant improvement in OS with zibotentan monotherapy in men with mildly symptomatic CRPC [61]. Moreover, the ENTHUSE M0 trial of zibotentan monotherapy in patients with nonmetastatic CRPC has been discontinued following an early efficacy review by the independent DMC indicating that the trial was unlikely to meet its primary efficacy end points [OS and progression-free survival (PFS)] [62]. Phase III results for zibotentan/docetaxel treatment of bone metastatic CRPC are still pending.

SRC inhibitors

The nonreceptor tyrosine kinase SRC is the prototypic member of the SRC family kinases (SFKs), which have established roles in tumor development, pathogenesis of visceral and bone metastases [63–65], and regulation of normal osteoclast function [66–68]. In a retrospective analysis, patients with prostate cancer whose tumors had elevated SRC activity had a significantly shorter time to relapse/crastion resistance and shorter survival. Additionally, SRC activity was higher in tumors that subsequently metastasized to bone [69].

SRC inhibitors with preclinical antitumor and antiosteoclast activity, include dasatinib, saracatinib, and bosutinib. Dasatinib inhibits prostate cancer cell adhesion, migration, and invasion at clinically achievable concentrations, and in an orthotopic nude mouse model, prostate tumors from dasatinib-treated mice had significantly lower weight than tumors from control mice [69–71]. Dasatinib also showed inhibitory activity against bone regulatory mechanisms, including osteoclastogenesis, prostate cancer cell-induced osteoclast differentiation and activity, and osteoblast proliferation [72–76]. In vivo, dasatinib inhibited growth of prostate cancer cells implanted into bone, and dasatinib combined with docetaxel significantly decreased
both circulating PSA levels and tumor growth in bone more than docetaxel alone [77]. Saracatinib inhibited androgen-dependent and androgen-independent prostate cancer cell proliferation, in vitro migration, and in vivo tumor growth [78, 79]. Saracatinib also inhibited human osteoclast differentiation and osteoclast-mediated bone resorption in vitro [80]. Bosutinib has been shown to decrease SRC activation, proliferation, migration, and invasion of prostate cancer cells. In vivo, bosutinib significantly reduced prostate tumor growth and skeletal lesions [81].

Clinical trials have assessed several SRC inhibitors in CRPC. In a phase II trial in patients with chemotherapy-naive CRPC and increasing PSA levels (n = 48), single-agent dasatinib (100 mg once daily, qd) had modest antitumor activity; after 12 and 24 weeks of therapy, 21 (44%) and 8 (17%) patients remained free from progressive disease. Most assessable patients with bone metastases had decreased urinary NTX levels (51% of patients had a ≥40% decrease) and BAP levels (59% of patients). The most frequent treatment-related adverse events (AEs) (≥20%) were fatigue, nausea, diarrhea, headache, and anorexia, and six patients (13%) had grade 3–4 side-effects [82]. In a phase II trial in CRPC, dasatinib combined with docetaxel was generally well tolerated and showed promising activity. Lack of disease progression was seen in 44% of patients at week 12 and 17% at week 24 and decreased BAP and urinary NTX (≥40% from baseline) in 59% and 51%, respectively [82]. Based on these results, a phase III randomized study comparing docetaxel plus dasatinib to docetaxel plus placebo in CRPC has been initiated (CA180-227; NCT00744497).

In a phase I study of saracatinib in healthy men, large decreases in serum markers of bone resorption were recorded [83]. In a phase II clinical trial of saracatinib monotherapy (175 mg qd) in 28 patients with CRPC, 5 patients had a transient PSA reduction, but bone markers were not evaluated [84]. An ongoing phase II study will compare effects of saracatinib or zoledronic acid plus standard of care on bone turnover in patients with bone metastatic breast or prostate cancer (NCT00558272).

thalidomide and derivatives

Thalidomide and its derivatives, lenalidomide and pomalidomide, are potent anti-inflammatory, antiangiogenic, and immunomodulatory drugs with the potential to interfere with several bone metastatic microenvironment components [85]. In vitro, thalidomide selectively inhibited androgen receptor-positive prostate cancer cell growth and reduced PSA secretion by 70%, while pomalidomide and lenalidomide with or without docetaxel significantly increased apoptosis in prostate cancer cells cocultured with peripheral blood mononuclear cells (PBMC) [86, 87]. Furthermore, pomalidomide inhibited osteoclastogenesis and lenalidomide suppressed osteoclast differentiation in vitro [88, 89].

In a randomized phase II study of docetaxel with or without thalidomide in patients with metastatic CRPC, PSA response rate (53% versus 37%) and median OS (29 versus 15 months) were higher in the thalidomide arm; however, no patient with bone lesions achieved normalized bone scans [90]. Thalidomide has also been assessed in a phase II trial combined with docetaxel, bevacizumab, and prednisone in patients with progressive metastatic CRPC. PSA declines of ≥50% were seen in 90% of patients who received combination therapy, with 88% achieving a ≥30% PSA decline within the first 3 months of treatment. Median TTP was 18.3 months and median OS was 28.2 months for the combination arm [91]. Initial efficacy data have been reported from phase I studies of lenalidomide monotherapy and combination therapy in CRPC. Nine of 35 patients with refractory CRPC who received lenalidomide monotherapy had SD [92]. In addition, two of seven assessable patients treated with lenalidomide plus paclitaxel had a PSA response [93]. A phase III study of docetaxel with or without lenalidomide in patients with metastatic CRPC is ongoing (NCT00988208).

cabozantinib

Cabozantinib (XL184) is an oral MET [hepatocyte growth factor (HGF) receptor] and VEGFR2 inhibitor. MET and/or HGF overexpression are associated with prostate cancer metastasis, and in preclinical studies, androgen ablation up-regulated MET signaling, promoting tumor growth, invasion, and metastasis [94, 95]. Preliminary data from a phase II randomized discontinuation trial in patients with measurable CRPC with or without bone metastases that had progressed after systemic chemotherapy have been presented. Of 171 assessable patients, 43% had received prior docetaxel and 87% had bone metastases. At 12 weeks, 4% of patients had a confirmed tumor response and 79% had SD. Of patients with measurable soft tissue lesions and at last one post-baseline assessment (n = 151), 74% showed some evidence of tumor regression, therefore, randomization was suspended. Cabozantinib significantly improved median PFS compared with placebo [21 versus 6 weeks, respectively; hazard ratio (HR) 0.13, P = 0.0007]. Median post-randomization PFS was 29 weeks in docetaxel-naive patients (n = 90) and 24 weeks in docetaxel-pretreated patients (n = 64). Of 108 bone scan assessable patients, 75% had complete or partial resolution of bone scans and 21% had stable scans. Of 83 patients with painful bone metastases, 67% had improved bone pain. A majority of patients had reductions in bone markers. However, there is currently a lack of functional data (changes in markers indicating bone metabolic or antitumor effects) that could explain improved bone scans seen with cabozantinib.

Thalidomide has also been assessed in a phase II trial combined with docetaxel, bevacizumab, and prednisone in patients with progressive metastatic CRPC. PSA declines of ≥50% were seen in 90% of patients who received combination therapy, with 88% achieving a ≥30% PSA decline within the first 3 months of treatment. Median TTP was 18.3 months and median OS was 28.2 months for the combination arm [91]. Initial efficacy data have been reported from phase I studies of lenalidomide monotherapy and combination therapy in CRPC. Nine of 35 patients with refractory CRPC who received lenalidomide monotherapy had SD [92]. In addition, two of seven assessable patients treated with lenalidomide plus paclitaxel had a PSA response [93]. A phase III study of docetaxel with or without lenalidomide in patients with metastatic CRPC is ongoing (NCT00988208).

agents targeting bone stroma

radiopharmaceuticals

Radiopharmaceuticals, such as samarium-153 (153Sm), strontium-89 (89Sr), and radium-223 (223Ra), localize to areas of osteoblastic activity, irradiating tumor cells and cytokine-secreting cells that mediate bone pain [97]. A randomized phase II trial in chemosensitive CRPC (n = 103) demonstrated
that doxorubicin plus \(^{89}\)Sr significantly improved OS compared with doxorubicin alone (28 versus 17 months, \(P = 0.0014\); 52% of patients with bone pain also had complete resolution of pain [98]. In a phase II trial of docetaxel plus \(^{153}\)Sm in chemo-sensitive CRPC \((n = 43)\), PSA response rate was 77%, median OS was 29 months, and 76% of patients had a ≥20% decline in pain level [99]. In a randomized phase II study, a higher proportion of \(^{223}\)Ra-treated patients had reduced BAP levels compared with placebo (66% versus 9% BAP reduction), and median OS was 65 versus 46 weeks [100]. Normalization of BAP levels following \(^{223}\)Ra treatment was significantly associated with a dose-dependent increase in median OS [101]. The phase III ALSYMPCA study assessing efficacy and safety of \(^{223}\)Ra plus best standard of care (BSC) compared with placebo plus BSC in patients with symptomatic bone metastases in CRPC has been stopped early due to a significant treatment benefit surpassing the predefined OS threshold. OS for patients in the \(^{223}\)Ra arm was 14.0 and 11.2 months for placebo \((P = 0.00185, \text{HR} = 0.695, 95\% \text{ confidence interval } 0.552-0.875) [102]. A randomized phase III study assessed \(^{153}\)Sm-leixidronam versus nonradioactive \(^{153}\)Sm-leixidronam in patients with CRPC and painful bone metastases. Compared with \(^{152}\)Sm-leixidronam, \(^{153}\)Sm-leixidronam significantly reduced pain scores and opioid analgesic use after 3–4 weeks \((P < 0.0284)\). Bone marrow suppression associated with \(^{153}\)Sm-leixidronam was mild, recovering to baseline within 8 weeks [103]. Another randomized phase III trial \((\text{NCT00024167})\) is comparing survival in patients with CRPC and bone metastases following chemotherapy with or without \(^{89}\)Sr.

Recently, a press release has reported that a randomized phase III trial of men with CRPC and symptomatic bone metastases of \(^{223}\)Ra \((\text{NCT00699751})\) has met its primary end point of improved OS. Full data are awaited.

denosumab

Denosumab is a fully human monoclonal antibody directed against RANKL, a key mediator of osteoclast formation, function, and survival. Denosumab efficacy against CRPC bone metastases was initially assessed in a phase II study. Fifty patients with increased urinary NTX levels despite prior zoledronic acid treatment were randomized to either continue on bisphosphonates or receive subcutaneous denosumab. Denosumab normalized NTX levels more frequently than continuing bisphosphonate treatment and a lower proportion of patients in the denosumab group experienced SREs [104].

A phase III trial has demonstrated superiority of denosumab \((n = 950)\) over zoledronic acid \((n = 951)\) in delaying/preventing SREs (times to first on study SRE were 20.7 versus 17.1 months, for denosumab and zoledronic acid, respectively; \(\text{HR} = 0.82, P = 0.008\)) and significantly suppressed both urinary NTX and BAP compared with the zoledronic acid arm \((P < 0.0001\text{ for both}) [105]\). This was the last of three pivotal trials exploring denosumab treatment of bone metastases that formed the basis of FDA approval of denosumab for preventing SREs in patients with bone metastases from solid tumors. Denosumab is the most efficient agent for targeting the bone microenvironment in patients with CRPC approved to date.

agents targeting the immune system

An alternative to agents specifically targeting regulatory mechanisms of tumors or their interaction with bone stroma is the use of immunotherapies. Immune cells residing in the bone marrow can accumulate in the tumor microenvironment where they release factors regulating tumor growth, survival, angiogenesis, and invasion. Cancer cells can evade the immune system through multiple mechanisms and research has focused on targeting the immune system either by directly enhancing tumor cell immunogenicity or inducing a more effective antitumor immune response [19]. Trials of immunotherapies in patients with prostate cancer have yielded promising survival results, but effects on bone tumor microenvironment have not yet been reported.

Sipuleucel-T has proved effective against asymptomatic or minimally symptomatic metastatic CRPC. Treatment with sipuleucel-T involves harvesting patient-derived autologous PBMCs, including antigen-presenting cells, which are activated \(\text{ex vivo}\) before readministration to the patient. Activation is achieved using a recombinant fusion protein composed of prostatic acid phosphatase linked to granulocyte–macrophage colony-stimulating factor. Following a phase III clinical program demonstrating a survival benefit for patients treated with sipuleucel-T compared with control (nonactivated PBMC) \((\text{median survival: } 25.8 \text{ versus } 21.7\text{ months, } \text{HR } 0.77, P = 0.032)\), sipuleucel-T was FDA approved for treating asymptomatic or minimally symptomatic metastatic CRPC [107].

A prostate cancer vaccine, PROSTVAC-VF, has also been developed. The vaccine comprises two recombinant viral vectors each encoding transgenes for PSA and three immune costimulatory molecules \((B7.1, \text{intercellular adhesion molecule 1}, \text{and lymphocyte function-associated antigen 3})\). Results from a phase II randomized study in patients with mildly symptomatic metastatic CRPC \((114/122 \text{ with bone metastases})\) indicated that at 3 years after study, 30% of vaccine-treated patients were alive compared with 17% of the control group \((\text{median survival } 25.1 \text{ versus } 16.6\text{ months, respectively}) [108]\).

Another potential immunotherapeutic approach to treating CRPC is to stimulate T-cell CTLA-4 receptors to potentiate T-cell-mediated immunity and antitumor responses. A pilot trial of the human anti-CTLA-4 antibody, ipilimumab, in 14 patients with metastatic CRPC showed that ipilimumab was well tolerated, and two patients had a PSA response [109]. More recently, ipilimumab was shown to act synergistically with androgen ablation in patients with advanced prostate cancer; 30/54 patients had undetectable PSA by 3 months [110]. Three phase III trials are currently recruiting patients to assess efficacy of ipilimumab monotherapy in patients with advanced chemotherapy-naïve \((\text{NCT01057810})\) or docetaxel-pretreated \((\text{NCT00861614})\) CRPC and to assess OS in patients with advanced prostate cancer treated with...
ipilimumab plus radiotherapy compared with radiotherapy alone (NCT00861614).

antiangiogenic agents

Angiogenesis plays an important role in tumorigenesis, proliferation, and metastasis of prostate cancer and other solid tumors. The bone microenvironment is a rich source of proangiogenic cytokines including VEGF and platelet-derived growth factor (PDGF), both of which are secreted by tumor and stromal cells. Various antiangiogenic agents have been investigated in patients with prostate cancer, including bevacizumab, sunitinib, afibercept, and thalidomide and its analogs, although effects on the bone microenvironment have not been assessed or reported to date.

Bevacizumab is a humanized monoclonal antibody that blocks binding of VEGF to its receptors. Early preclinical studies showed that bevacizumab completely suppressed prostate cancer–induced angiogenesis and prevented tumor growth [111]. In a phase II study of 20 patients with CRPC and bone metastases, 11 patients had a PSA response to bevacizumab and docetaxel, including 7 who had previously responded to docetaxel alone [112]. In a phase III study in 1050 patients with chemotherapy-naive metastatic CRPC, bevacizumab plus docetaxel improved PFS, measurable disease response, and post-therapy PSA declines compared with placebo but did not improve OS (primary end INS> point) and was associated with increased morbidity and mortality [113]. A phase II trial assessed the combination of bevacizumab, thalidomide, docetaxel, and prednisone. Within the first 3 months of treatment, 88% of patients had a 30% decrease in PSA levels and median OS was 28 months [91].

Sunitinib is a multitargeted receptor tyrosine kinase inhibitor that inhibits the VEGF receptor among others. A preclinical human prostate cancer cell xenograft study found that daily treatment with single-agent sunitinib markedly reduced tumor volume and that combination with low-dose docetaxel (10 mg/kg) had similar activity to single-agent high-dose docetaxel (30 mg/kg) but with less toxicity [114]. In a phase II study of single-agent sunitinib in CRPC, 4/36 patients had a ≥50% PSA decline and 7/36 had a ≥30% PSA decline. However, a high rate of discontinuation of therapy for toxicity suggested that lower dose sunitinib and less heavily pretreated population may provide a more suitable evaluation [115]. The phase III trial of second-line sunitinib plus prednisone following docetaxel failure (SUN 1120, NCT00676650) was stopped by the DMC at the second interim analysis for futility (no improvement in OS) despite improved PFS in the sunitinib plus prednisone arm [116]. A phase III trial of afibercept plus docetaxel in chemotherapy-naive patients (VENICE, NCT00519285) is ongoing.

A preclinical study has demonstrated the potential of the anti-PDGFRα monoclonal antibody IMC-3G3 as a single agent or combination therapy for prostate cancer bone metastases [117]. A clinical trial (NCT01204710) is currently recruiting patients with metastatic CRPC that has progressed or is intolerant to docetaxel-based therapy to assess the safety and efficacy of IMC-3G3 combined with mitoxantrone plus prednisone compared with mitoxantrone plus prednisone.

conclusions

Clinical presentation of patients with CRPC is associated with a high frequency of bone metastases, characterized radiologically by an osteoblastic phenotype and biologically by a high bone turnover, including both high osteolysis and osteogenesis. Complications due to bone metastases are responsible for a significant proportion of the morbidity and mortality associated with advanced prostate cancer. To improve patients’ QoL or survival, interactions between prostate cancer cells and the surrounding bone stroma must be understood. Drugs targeting the bone metastatic microenvironment may be particularly beneficial for treating prostate cancer. In this regard, agents that inhibit osteoblast/osteoclast differentiation or activity, tumor cell proliferation, migration or invasion, angiogenesis, or modulate the immune system are currently being investigated, either as single agents or in combination with cytotoxic drugs. Although preclinical studies and clinical data have shown that bisphosphonates, radiopharmaceuticals, RANKL inhibitors, ET receptor inhibitors, and SRC inhibitors can inhibit components of the bone metastatic microenvironment, as shown by reductions in incidence of SREs, palliation of bone pain and modulation of bone turnover biomarkers, microenvironment-specific effects by agents directed against the immune system or angiogenesis have not yet been reported, although a favorable effect of sipuleucel-T on OS was demonstrated. Conclusive data from randomized phase III trials are needed to show that inhibiting the bone metastatic environment can improve survival of patients with CRPC, and several trials are ongoing that could eventually provide this proof of principle. As further data from studies investigating the extent of bone microenvironment modification become available (e.g., through routine incorporation of bone-related end points), agents that target the bone tumor microenvironment are likely to become an increasingly important component of CRPC treatment.

acknowledgements

The authors take full responsibility for the content of this article and confirm that it reflects their viewpoint and medical expertise. StemScientific, funded by Bristol-Myers Squibb, provided writing and editing support. Bristol-Myers Squibb did not influence the content of the manuscript nor did the authors receive financial compensation for authoring the article.

disclosure

YL and CM have no conflicts of interest to declare. KF has acted as an advisory or speaker for Amgen, Novartis, Astrazeneca, Sanofi-Aventis, Bristol-Myers Squibb, Ipsen, Keocyt, and Janssen.
references


89. Munemasa S, Sakai A, Kuroda Y et al. Osteoprogenitor differentiation is not affected by immunomodulatory thalidomide analogs but is promoted by low


