Targeting bone metastases in prostate cancer: improving clinical outcome

Jean-Jacques Body, Sandra Casimiro and Luís Costa

Abstract | Bone metastases develop in most patients with metastatic castration-resistant prostate cancer (mCRPC). They affect the structural integrity of bone, manifesting as pain and skeletal-related events (SREs), and are the primary cause of patient disability, reduced quality of life (QOL) and death. Understanding the pathophysiology of bone metastases resulted in the development of agents that improve clinical outcome, suggesting that managing both the systemic disease and associated bone events is important. Historically, the treatment of CRPC bone metastases with early radiopharmaceuticals and external beam radiation therapy was largely supportive; however, now, zoledronic acid and denosumab are integral to the therapeutic strategy for mCRPC. These agents substantially reduce skeletal morbidity and improve patient QOL. Radium-223 dichloride is the first bone-targeting agent to show improved survival and reduced pain and symptomatic skeletal events in patients with mCRPC without visceral disease. Five other systemic agents are currently approved for use in mCRPC based on their ability to improve survival. These include the cytotoxic drugs docetaxel and cabazitaxel, the hormone-based therapies, abiraterone and enzalutamide, and the immunotherapeutic vaccine sipuleucel-T. Abiraterone and enzalutamide are able to reduce SREs and improve survival in this setting. Novel agents targeting tumour and bone cells are under clinical development.

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Introduction

Prostate cancer is the second most frequently diagnosed cancer and the fifth leading cause of cancer-related death in men, accounting for an estimated 15% (1.1 million) of all new cancer cases and 7% (307,000) of all cancer-related deaths in men worldwide in 2012.[1]

Androgen-dependent prostate tumour growth is controlled by surgical or medical castration. The drug classes used in medical castration or androgen deprivation therapy (ADT) include luteinizing hormone-releasing agonists or antagonists, and antiandrogens. This strategy is the standard of care for patients with advanced or metastatic disease and it is continued after castration levels of testosterone have been confirmed.[2,3] Patients remain on ADT throughout the course of their disease. In many men, the disease will progress, despite castration levels of testosterone, to become castration-resistant prostate cancer (CRPC).[2,4]

The majority (around 90%) of patients with metastatic CRPC (mCRPC) have radiological evidence of bone metastases, and bone is the first metastatic site in 80% of patients.[5,6] Bone metastases lead to changes in the structural integrity of the bone and manifest as pain and debilitating skeletal-related events (SREs, Box 1) and are the primary cause of disability, reduced quality of life (QOL) and death.[7,8] The extent of bone involvement in mCRPC negatively correlates with patient survival.[9] SREs are also associated with reduced patient survival: in a Danish population-based study in men with prostate cancer, one-year survival was 87% in men without bone metastases, 47% in those with bone metastases but no SREs, but only 40% in those with bone metastases and SREs.[10]

Currently, six therapies are approved for the treatment of mCRPC, based on their capacity to improve overall survival in randomized controlled trials. These include the cytotoxic drugs docetaxel[11,12] and cabazitaxel,[13] the immunotherapeutic vaccine sipuleucel-T,[14] and the hormone-based therapies abiraterone[15–17] and enzalutamide.[18,19] In 2013, the bone-targeting radiopharmaceutical radium-223 dichloride (^{223}Ra) was added to this list.[20] Other bone-targeting agents are used in the supportive care of patients with mCRPC to reduce pain and the incidence of SREs, including osteoclast inhibitors such as zoledronic acid[21,22] and denosumab,[23] which have been shown to have the highest efficacy in delaying and reducing skeletal complications of mCRPC in comparison with other drugs.

Pain relief for bone metastases can be achieved with radiotherapy. External beam radiation therapy (EBRT) is recommended for patients with focal metastases.[2] Bone-targeting radiopharmaceuticals incorporated into new bone during turnover and remodelling at metastatic sites can be effective for patients with multiple metastases, and include β-particle-emitting radioisotopes, strontium-89 (^{89}Sr), samarium-153 (^{153}Sm) and rhenium-186 (^{186}Re), and α-particle-emitting ^{223}Ra.[24,25] In the treatment of

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Key points

- Bone metastases are common in metastatic castration-resistant prostate cancer (mCRPC) and lead to skeletal-related events (SREs), which are a major cause of patient disability, reduced quality of life, and death
- Understanding the pathophysiology of bone metastasis resulted in the approval of agents that improve clinical outcomes in patients with mCRPC, and new targeted agents are under development in this setting
- Managing both the tumour and associated SREs is important to improve survival and quality of life of patients with mCRPC
- Osteoclast inhibitors are part of the standard treatment of CRPC metastatic to bone; denosumab has been shown to reduce skeletal morbidity more than zoledronic acid
- New antitumour agents increase survival and some, such as abiraterone and enzalutamide and ^{223}Ra, also decrease skeletal morbidity
- Ongoing clinical studies are investigating the optimal position and combinations of approved agents in the treatment paradigm to maximize patient benefit in this setting

Box 1 | Definitions of skeletal events in mCRPC

Skeletal-related events[22,23]

- Pathological fracture (confirmed by serial radiological review)
- Radiation therapy to bone
- Surgery to bone
- Spinal cord compression (confirmed by serial radiological review)
- Change in antineoplastic therapy to treat bone pain*

Symptomatic skeletal events[20]

- Use of external beam radiation therapy to relieve skeletal symptoms
- Symptomatic bone fracture
- Surgery to bone
- Symptomatic spinal cord compression

*Parameter used only in Saad *et al.*[21,22] Abbreviation: mCRPC, metastatic castration-resistant prostate cancer.

patients with mCRPC and bone metastases, the approval of ^{223}Ra is an important development, as this agent is the first bone-targeting α-particle-emitting radiotherapeutic to demonstrate a survival advantage in addition to reducing symptomatic skeletal events (SSEs) and associated pain.[20,26,27] Thus, targeting bone metastases in patients with mCRPC offers a new treatment approach to improve survival in this setting. A better understanding of the pathophysiology of bone metastases has led to the development of agents that can both improve long-term outcomes and reduce the pain and skeletal morbidity associated with this condition.

In this Review, we describe the pathophysiology of prostate cancer bone metastases (PCBMs) and the clinical burden of skeletal metastases in this setting. We review the clinical data from studies of bone-targeting agents in the palliative care of patients with mCRPC, including bisphosphonates, β-particle-emitting radiopharmaceuticals and denosumab. We focus in particular on the development of ^{223}Ra, a bone-targeting agent with effects on both skeletal and long-term outcomes. In this context, we further review the properties of both approved and novel systemic agents with regard to improving skeletal outcomes. Finally, we discuss the place of these agents in the overall therapeutic strategy for patients with mCRPC.

Bone metastasis in CRPC

Prostate cancer has a propensity to metastasize to bone. In an analysis of 1,589 autopsy reports of men older than 40 years with prostate cancer, 35% of men had evidence of metastases, with the most frequent involvement (90%) being in bone.[5] The most common sites for PCBMs are the ribs, spine and pelvis, although metastases in the skull and long bones have also been reported.[28–30] The high prevalence of bone metastases in patients with mCRPC adds to the burden of the disease. Bone metastases cause substantial skeletal morbidities, including severe bone pain (requiring strong analgesics or EBRT), pathological fracture, spinal cord or nerve root compression, hypocalcaemia (often asymptomatic) and myelosuppression.[31,32] As a result of these morbidities, patient QOL—including physical, emotional and functional wellbeing—is substantially reduced.[8] Furthermore, metastasis-associated skeletal morbidities are negative predictors of survival in patients with mCRPC.[9,33–35] Overall skeletal morbidity incurs marked increases in the costs of treating patients with bone metastases.[36–38] Reducing the incidence of SREs or prolonging the time to occurrence of SREs is important in improving clinical outcome in patients with mCRPC and reducing the financial burden of the disease. Thus, regulatory authorities request the inclusion of SREs, and more recently SSEs, as clinical end points in the evaluation of new therapeutic agents in this setting.[20–23,26]

Pathological fractures constitute a classical feature of SREs, although they occur much less frequently as a result of bone metastases in mCRPC than in metastatic breast cancer.[22,39] In clinical trials of bone-targeting agents, the occurrence of SREs has most often been monitored through periodic radiological review.[21–23] Clinically identified SSEs differ from asymptomatic radiologically detected fractures, and can be viewed as more clinically relevant (Box 1). The main difference between SREs and SSEs lies in their assessment. For SREs, patients have a full systematic radiological survey every 4 weeks or 8 weeks to detect asymptomatic pathological fracture and spinal cord compressions. By contrast, detection of SSEs does not include serial radiological review; fractures and spinal cord compressions are assessed based on patient symptoms and are therefore identified clinically.

SSEs are considered to be more relevant to daily routine clinical care than classical SREs. Not surprisingly, the use of SSEs as an end point is becoming more common in clinical trial design. In 2013 and 2014, time to first SSE as an end point has been used in trials of bone-targeting agents shown to prolong overall survival.[20,26] The validation of SSEs as a suitable endpoint for clinical studies was demonstrated in a randomized phase III trial in patients with CRPC with bone metastases, in which denosumab was shown to reduce the risk of skeletal complications regardless of whether the end point was SREs or SSEs.[31]

Bone physiology

The health and structural integrity of normal bone is maintained by an active and continuous cycle of bone resorption by osteoclasts and new bone formation by osteoblasts. Osteoclasts differentiate from monocyte

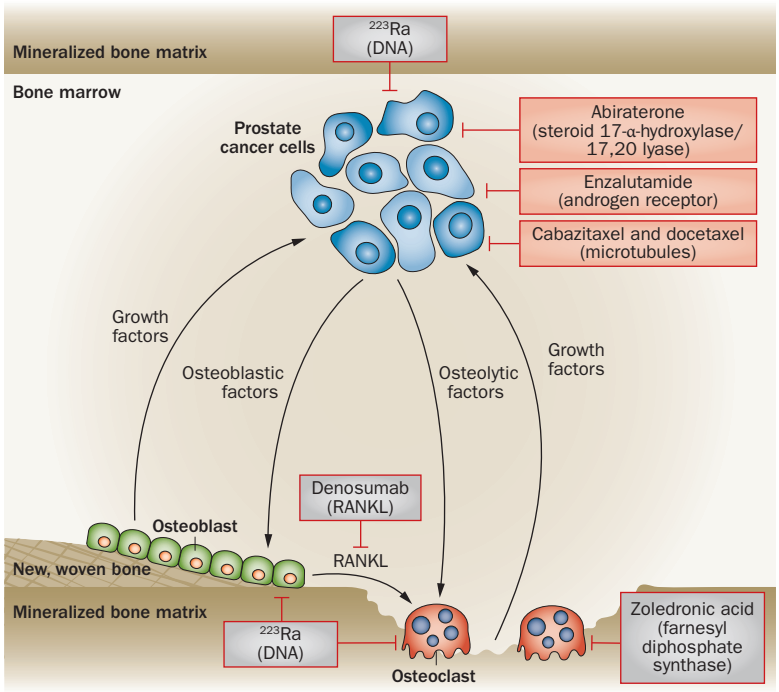

Figure 1 | The cyclic feedback loop between PCBMs, osteoblasts and osteoclasts, and target sites of therapeutics. PCBMs release osteoblastic growth factors, such as ET-1, which leads to formation of new bone (woven bone). In turn, osteoblasts release PCBMs-stimulating growth factors, for example TGF-β. In addition, stimulated osteoblasts release RANKL and PTH, which promote osteoclast activity, together with PCBMs-released osteolytic factors, including uPA and PTHrP. The resulting release of growth factors from the bone matrix promotes the establishment of further PCBMs. Currently approved drugs for patients with PCBMs act on PCBMs directly or inhibit osteoclast activity via different molecular targets. Abbreviations: ET-1, endothelin-1; PCBMs, prostate cancer bone metastases; PTH, parathyroid hormone; PTHrP, PTH-related protein; TGF-β, transforming growth factor β-1; uPA, urokinase-type plasminogen activator. Adapted with permission obtained from *Molecular and Cellular Endocrinology*, **310**, Casimiro, S. *et al.*, The critical role of the bone microenvironment in cancer metastases, 71–81, © (2009), with permission from Elsevier.

or macrophage precursors, mediated by the expression of cytokines including M-CSF, RANKL, IL-6, IL-8 and CCL2 (also known as C–C motif chemokine 2).[40,41] Osteoclasts attach to bone matrix to form a resorption vacuole, which they acidify and into which they secrete lytic enzymes. Bone resorption leads to the release of osteoblast-activating growth factors (including transforming growth factor β-1 [TGF-β], bone morphogenetic proteins [BMPs], fibroblast growth factors [FGFs], platelet-derived growth factors [PDGFs], IGF-I and IGF-II) from the bone matrix, which regulates osteoblast growth and differentiation. Osteoblasts differentiate from stromal mesenchymal stem cells mediated by the activity of the runt-related transcription factor 2 and the Wnt-signalling pathway.[40] Activated osteoblasts produce an organic matrix, which is mineralized over the course of several weeks.

At the molecular level, RANKL, its receptor (RANK) and osteoprotegerin (OPG) are crucial for normal bone physiology; the RANKL–RANK–OPG axis is the key regulator of the interactions between osteoblasts and osteoclasts.[41,42] RANK is a transmembrane protein expressed on the surface of osteoclast precursor cells and its ligand RANKL is produced by osteocytes, osteoblasts and bone marrow stromal cells. Binding of RANKL to RANK leads to stimulation of RANK signalling, which regulates osteoclast differentiation, activity and survival. This process is balanced by OPG, a soluble decoy receptor for RANKL, which is produced by mature osteoblasts and stromal cells. OPG binds RANKL on the surface of osteoclast precursor cells and negates the ability of RANKL to activate RANK. In turn, osteoclast differentiation, activation and bone resorption are diminished. Increasing the ratio of OPG to RANKL leads to increased bone mass.[43] Thus, the physiology of normal bone involves interaction between osteoclasts, osteocytes, osteoblasts and the bone microenvironment.

Pathophysiology of bone metastasis

PCBMs fit the 'seed and soil' hypothesis, first observed by Paget in 1889, which describes that seeds (metastatic cells) only thrive if the soil environment (bone) is amenable to growth.[44] The bone microenvironment seems to facilitate prostate cancer cell growth, which subsequently leads to disruption of the normal balance of osteolytic and osteoblastic activity.[45] The establishment and expansion of prostate cancer metastases within bone involves paracrine signalling between tumour cells and the normal cells in the bone microenvironment.

Briefly, circulating prostate cancer cells are established in bone via entry through the wide-channelled sinusoids of the bone marrow cavity. This process requires a capability to migrate across the sinusoidal wall, invade the marrow stroma and travel to the endosteal bone surface. The SDF-1–CXCR-4 pathway seems to be important for homing and invasion of metastases to bone.[46,47] Tumour expression of the adhesion molecule integrin αvβ3, which binds the RGD peptide sequence found on extracellular matrix proteins, also seems to be important for invasion of the bone endosteum.[48] In addition, activated RANK–RANKL signalling in prostate cancer cells is implicated in their colonization of bone during metastasis.[49,50]

Within the bone microenvironment, prostate cancer cells acquire properties of bone cells, expressing transcription factors, including OSF-2, and interacting with bone marrow stem cells and haematopoietic cells in the metastatic niche to promote tumour growth.[45]

The interaction between prostate cancer cells and the bone microenvironment exists as a cyclic feedback loop (Figure 1). Growth factors released by PCBMs stimulate osteoblast activity and new bone formation. Tumour-produced endothelin-1 (ET-1) stimulates osteoblasts via the endothelin A receptor.[51] ET-1 activates Wnt signalling through the suppression of the Wnt antagonist Dkk-1, which is secreted in an autocrine regulatory loop by osteoblasts. Dkk-1 promotes osteolytic metastases in addition to modulating the development of osteoblastic metastases.[52] Other tumour-secreted osteoblast-stimulating growth factors include adrenomedullin, FGFs, PDGFs and BMPs.[40,42,53] Tumour-secreted

proteases (matrix metalloproteinases [MMPs], prostate-specific antigen [PSA], and urokinase-type plasminogen activator [uPA]) lead to the release of osteoblastic promoting growth factors from the extracellular matrix, including TGF-β and IGF-I.[42,53]

TGF-β is also deposited into the bone matrix by mature osteoblasts. However, the role of TGF-β in regulating bone formation and resorption is complex. For example, during early stages of differentiation, osteoblasts are sensitive to the mitogenic effects of TGF-β, whereas in later stages of their differentiation TGF-β can block the maturation of osteoblasts and bone mineralisation.[54,55]

Increased tumour-induced osteoblast activity also leads to increased RANKL concentrations and hypocalcaemia, which leads to parathyroid hormone (PTH) release, both inducing osteoclast activity. Osteoclast activity is key in the establishment of PCBMs and the resultant release of growth factors from bone matrix promotes the establishment of prostate cancer cells, further feeding the 'vicious cycle' of bone growth and breakdown.

Prostate cancers have also been shown to overexpress PTH-related protein (also known as PTH-related peptide, PTHrP), which is an important stimulator of osteoclast activity.[53,56] PTHrP is produced both by cancer cells and by cells within the bone microenvironment.[53] Increased PTHrP and IL-11 concentrations in the local environment drive RANKL expression and inhibit OPG secretion from osteoblasts and stromal cells, thereby activating osteoclastogenesis via the RANK receptor expressed on osteoclast precursor cells. Activated osteoclasts lead to bone resorption and further release of growth factors embedded in the bone matrix, stimulating tumour cell proliferation. Calcium released into the local bone environment during osteolysis might also contribute to growth and survival signals for the tumour cells. However, the role of PTHrP in PCBMs is controversial. PTHrP expression from prostate cancer cells can also have anabolic effects on bone.[57] Data from *in vitro* studies suggest that PSA cleaves PTHrP, converting it from an osteoclastic to an osteoblastic factor, although supporting *in vivo* studies are lacking.[53]

Clearly, osteolysis is important for the establishment of bone metastases and, once established, bone metastases facilitate osteolysis, but they also have an associated component of unregulated and increased bone formation during their aetiology and expansion. Thus, radiographic patterns of bone metastases are varied, ranging from osteolytic or mixed lesions in most types of cancers to predominantly osteoblastic lesions characteristic of prostate cancer.[42,56] Complex phenotypes often arise; mixed osteoblastic and osteolytic lesions can occur in a single patient.[58]

Osteoblastic activity from PCBMs is demonstrated by the detection of new woven bone (which has a dense appearance on radiographs), the increased uptake of bone scanning agents at lesion sites and raised bone-specific alkaline phosphate (BALP) levels in the serum of affected patients.[59] The presence of woven bone is confirmed by histology and histomorphometry.[58] The importance of osteolysis in the metastatic process is evidenced by histomorphometric studies and increased detection of bone resorption markers, such as urinary n-telopeptide (uNTx).[59] Increased bone resorption is suggested to be a prerequisite for successful seeding of metastatic cells even in osteoblastic-predominant bone metastases.[60] In preclinical models of prostate cancer, inhibition of osteoclasts can prevent bone metastases.[53] Prostate-cancer-induced woven bone is comprised of loosely packed, randomly orientated collagen bundles. Such bundles produce bone of suboptimal strength compared with mature, healthy bone, which is formed of lamellar bone comprised of collagen bundles packed in a linear fashion, resulting in optimum bone strength. Thus, the combination of inferior bone production and underlying osteolysis predisposes patients with PCBMs to fractures.[61]

Identifying biological and molecular mechanisms involved in the pathophysiology of PCBMs has led to the development of the therapeutic agents currently approved for treatment of patients with the disease. These agents act at different sites in the bone (Figure 1). However, our understanding of the mediators of important processes for prostate cancer cell metastasis (including the premetastatic niches, dissemination and homing of cancer cells, the establishment of prostate cancer cells within the bone, cancer cell dormancy in the bone and the vicious cycle) is clearly evolving.[62–66] Advances in our understanding of these processes offer potential for new treatments in patients with PCBMs.

Persistent prostate-cancer-induced bone pain is also a complex process: it comprises components of neuropathic, inflammatory and ischaemic pain, arising from ectopic sprouting and sensitization of primary afferent sensory nerve fibres within prostate-cancer-invaded bones. It is established and maintained through the cross talk that occurs between PCBMs, the bone matrix (osteoblasts and osteoclasts) and factors associated with the bone microenvironment.[67] The complexity of the interplay between tumour cells, peripheral nerves and bone cells makes the associated pain difficult to manage.[68] Tumour-produced ET-1 activates endothelin receptors on bone sensory nerve endings. Other receptors expressed on nociceptive nerve endings include TrK-A, Trpv1 and CGRP. Blockade of the endothelin A receptor and TrK-A has been shown to reduce pain associated with bone metastases.[56]

Bone-targeting therapies for mCRPC

In this Review, bone-targeting agents are defined as those compounds in clinical use that act primarily within bone. Here, we review the clinical development of bone-targeting agents approved for the treatment of patients with mCRPC and bone metastases and provide an overview of the effect of these agents in key randomized studies on selected skeletal outcomes (time to SRE and/or SSE) and survival (Table 1). A detailed summary of the efficacy of bone-targeting agents, including end points measuring pain, QOL and markers of bone turnover, is provided in Supplementary Table 1 online.

Table 1 | Skeletal outcome and overall survival in randomized studies of bone-targeting and disease-modifying agents

Agent	Study	Treatment arms (*n*)	Time to first SRE or SSE* Median (months), HR [95% CI]	Overall survival Median (months), HR [95% CI]
Bone-targeting agents				
Zoledronic acid	Saad *et al.* (2002 & 2004)[21,22]	Zoledronic acid (214) vs placebo (208)	16.0 vs 10.5,‡ 0.677 [0.505–0.908], *P*=0.009	17.9 vs 15.2,‡ *P*=0.091
Denosumab	Fizazi *et al.* (2011)[23]	Denosumab (950) vs zoledronic acid (951)	20.7 vs 17.1,§ 0.82 [0.71–0.95], *P*=0.0002 for non-inferiority, *P*=0.008 for superiority	19.4 vs 19.8, 1.03 [0.91–1.17], *P*=0.65
^{89}Sr	Porter *et al.* (1993)[94] Oosterhof *et al.* (2003)[99] (EORTC-GU group)	^{89}Sr vs placebo (126 in total) ^{89}Sr (101) vs local field radiotherapy (102)	NR NR	6.2 vs 7.8,‖ *P*=0.06 7.2 vs 11,§ 1.34 [1.01–1.75], *P*=0.0457
^{223}Ra	ALSYMPCA; Parker *et al.* (2013),[20] Sartor *et al.* (2014)[26]	^{223}Ra (614) vs placebo (307)	15.6 vs 9.8, 0.66 [0.52–0.83], *P*<0.001	14.9 vs 11.3,§ 0.70 [0.58–0.83], *P*<0.001
Disease-modifying agents				
Docetaxel	TAX 327; Tannock *et al.* (2004)[12]	Docetaxel q3w + prednisone (335) vs mitoxantrone q3w + prednisone (337)	NR	18.9 vs 16.5,§ 0.76 [0.62–0.94], *P*=0.009
	ASCENT; Beer *et al.* (2007)[125]	Docetaxel + calcitriol (125) vs docetaxel + placebo (125)	13.4 vs 11.9, 0.78 [0.57–1.074], *P*=0.13	NA vs 16.4, 0.67 [0.45–0.97], *P*=0.04
Cabazitaxel	TROPIC; de Bono *et al.* (2010)[13]	Cabazitaxel + prednisone (378) vs mitoxantrone + prednisone (377)	NR	15.1 vs 12.7, 0.70 [0.59–0.83], *P*<0.0001
Abiraterone	COU-AA-301; Fizazi *et al.* (2012),[16] Logothetis *et al.* (2012)[145]	Abiraterone + prednisone (797) vs placebo + prednisone (398)	25.0 vs 20.3, 0.615 [0.478–0.791] *P*=0.0001	15.8 vs 11.2, 0.74 [0.64–0.86], *P*<0.0001
	COU-AA-302;¶ Ryan *et al.* (2013)[17]	Abiraterone + prednisone (546) vs placebo + prednisone (542)	NR	NA vs 27.2,§ 0.75 [0.61–0.93], *P*=0.01
Enzalutamide	AFFIRM; Scher *et al.* (2012),[18] Fizazi *et al.* (2014)[19]	Enzalutamide (800) vs placebo (399)	16.7 vs 13.3, 0.69 [0.57–0.84], *P*<0.001	18.4 vs 13.6,§ 0.63 [0.53–0.75], *P*<0.001
	PREVAIL;¶ Beer *et al.* (2014)[149]	Enzalutamide (626) vs placebo (532)	31.1 vs 31.3, 0.72 [0.61–0.84], *P*<0.001	32.4 vs 30.2,§ 0.71 [0.60–0.84], *P*<0.001

A detailed summary of efficacy data is provided in Supplementary Table 1 online and Supplementary Table 2 online. For comparisons between trials, values have been converted using a time conversion calculator (http://www.calculatorsoup.com/calculators/conversions/time.php). *Time to first SRE has been most often used, except for time to first SSE in the ALSYMPCA study or skeletal-morbidity-free survival in the ASCENT study. ‡Conversion of days to months. §Study primary end point. ‖Conversion of weeks to months. ¶Performed in chemotherapy-naive patients. Abbreviations: NA, not achieved; NR, not reported; SSE, symptomatic skeletal event; SRE, skeletal-related event.

Osteoclast-targeting agents

Bisphosphonates

Bisphosphonates were the first and are the most widely used bone-targeting agents for the treatment of skeletal metastases. These agents are structurally similar to pyrophosphate and bind to hydroxyapatite crystals integrating into the bone matrix.[69] Nitrogen-containing bisphosphonates are potent inhibitors of farnesyl diphosphate synthase, leading to the blockade of protein isoprenylation and to an increase in osteoclast apoptosis.[70] Preclinical studies demonstrated that the nitrogen-containing bisphosphonates (notably zoledronic acid) were more potent in inhibiting osteoclast-mediated bone resorption compared with other bisphosphonates.[71] Other preclinical studies suggest that zoledronic acid might also affect prostate cancer cell adhesion and migration, and promote apoptosis in prostate cancer cells through the inhibition of tumour growth.[69,72]

In phase I studies in patients with solid tumours and bone metastases, zoledronic acid was found to be safe and potently inhibited bone resorption.[73,74] A randomized phase III trial in 643 patients with mCRPC and bone metastases without severe bone pain examined the effect of zoledronic acid (4 mg or 8 mg) given every 3 weeks for 22 cycles compared with placebo.[22] The dose was changed to 4 mg for all participants midway through the trial owing to concerns over renal impairment in the high-dose group. Treatment with zoledronic acid reduced the proportion of patients with SREs compared with placebo (primary end point, 33% versus 44%, *P*=0.021). After a follow-up period of 24 months, zoledronic acid compared with placebo decreased the risk of SREs by 36% and increased the time to first SRE, although no significant difference was reported in survival (Table 1).[21] Bone pain (as determined by pain score, brief pain inventory, and analgesic score) was significantly reduced in patients receiving zoledronic acid.

Several biochemical markers of bone metabolism were measured in urine and serum samples from study patients (Supplementary Table 1 online).[22] The uNTx:creatinine ratio, a measure of bone resorption, decreased by about 70% within 1 month of starting treatment with 4 mg zoledronic acid (95% CI −72.6% to −66.3%) and remained supressed. At the end of the study at 15 months, levels of serum BALP, a marker of osteoblastic bone formation activity, had increased significantly more in patients in the placebo group than in patients who received 4 mg zoledronic acid (33.7% versus 0.7%; *P*=0.001). Conversely, levels of serum PTH, a regulator of calcium homeostasis, were significantly higher in the patients who received 4 mg zoledronic acid compared with the placebo group (81.8% versus 17.1%; *P*=0.001). No difference between the groups was reported in disease progression, performance status or QOL.[22]

In 2002, zoledronic acid was approved by the FDA and the European Medicines Agency (EMA) for the prevention of SREs in patients with mCRPC. Interestingly, two studies published in 2014 did not corroborate the positive previous results. In the Alliance study (CALGB 90202), zoledronic acid failed to reduce the risk of SREs in patients with castration-sensitive prostate cancer and bone metastases.[75] Furthermore, in the ZEUS study, zoledronic acid was ineffective for the prevention of bone metastases in patients with high-risk localized prostate cancer.[76] The data from the Alliance and ZEUS studies in patients with early forms of the disease lend support to the view that bisphosphonates are only effective in patients with advanced mCRPC and bone metastases. Earlier randomized studies with two other, less potent, bisphosphonates (pamidronic acid and clodronic acid) failed to demonstrate efficacy of a level similar to zoledronic acid in patients with mCRPC.[77,78]

Denosumab

Denosumab, a human monoclonal antibody to RANKL, targets the RANKL–RANK–OPG axis during bone turnover. Denosumab prevents binding of RANKL to RANK on the surface of osteoclasts, preventing their differentiation and function and leading to the inhibition of bone loss (Figure 1).[79] Preclinical data also suggest that neutralisation of RANKL might inhibit prostate cancer metastasis to the bone.[49,50]

Data from phase I and phase II trials indicate that denosumab decreased bone resorption in patients with bone metastases from breast cancer and multiple myeloma.[80,81] The efficacy of denosumab therapy was notably assessed in patients with bone metastases whose uNTX levels were not responding to intravenous bisphosphonate therapy. In this study, 111 patients with breast cancer, prostate cancer or other solid tumours were randomized to subcutaneous denosumab or continued intravenous bisphosphonate therapy for 25 weeks.[82] The patients had elevated uNTx levels at screening before randomization, despite still receiving intravenous bisphosphonates, and so were not considered to be responding adequately to bisphosphonate therapy. Compared with patients continuing on intravenous bisphosphonate therapy, a higher proportion of patients receiving subcutaneous denosumab had decreased urinary uNTx levels (<50 nmol/l; 71% versus 29%) and they also had a lower incidence of SREs (8% versus 17%).[82]

An analysis of two phase II trials showed that denosumab suppresses bone resorption independently of prior bisphosphonate treatment—even in patients who did not normalize bone resorption under prior treatment.[83] A randomized, double-blind phase III trial compared denosumab with zoledronic acid in patients with CRPC and bone metastases.[23] Patients received either 120 mg subcutaneous denosumab plus intravenous placebo every 4 weeks or 4 mg intravenous zoledronic acid plus subcutaneous placebo every 4 weeks. In 950 patients receiving denosumab, median time to first SRE was significantly longer than in 951 patients receiving zoledronic acid (primary end point, 20.7 months versus 17.1 months; HR 0.82, 95% CI 0.71–0.95, $P = 0.008$). No difference in overall survival was reported (Table 1). Regarding exploratory end points, overall skeletal morbidity was lower in the denosumab group (Supplementary Table 1 online). Time to disease progression did not differ, and changes in median PSA concentrations and bone pain (based on Medical Dictionary for Regulatory Activities terms) were also similar between the treatment arms. At week 13, median decreases in bone marker turnover (uNTx and BALP) were significantly greater in patients receiving denosumab compared with zoledronic acid. The FDA and EMA subsequently approved the use of denosumab for the prevention of SREs in patients with mCRPC.[84,85]

Toxicity of osteoclast-targeting agents

Nephrotoxicity is the most commonly reported adverse event related to bisphosphonate treatment, especially following intravenous use. Monitoring serum creatinine levels before each dose, dose adjustment according to creatinine clearance and avoiding rapid infusion (infusion should not take <15 minutes) are required to reduce the risk of impaired renal function owing to zoledronic acid. Other potential toxic effects include self-limiting bone pain and flu-like symptoms, typically occurring after the first infusion.[86–88] By contrast, denosumab does not cause nephrotoxicity in men with prostate cancer and is safe regardless of renal function.[89]

Hypocalcaemia is most often asymptomatic with these agents; in the phase III trial in patients with CRPC and bone metastases, hypocalcaemia occurred more frequently with denosumab than with zoledronic acid (13% versus 6%; $P < 0.0001$).[23] In an integrated analysis of 5,723 patients from three randomized phase III trials, the safety profile for denosumab was better than for zoledronic acid, demonstrating no effect on renal function and no need for dose adjustment or renal monitoring.[90] In patients receiving denosumab the incidence of hypocalcaemia was higher than in patients receiving zoledronic acid (3.1% versus 1.3% for grade 3 or grade 4 toxicities), though most cases were asymptomatic.[90] Thus, repletion of vitamin D levels before the initiation of therapy and monitoring of calcium levels during therapy is recommended in the prescribing information of denosumab.[84,85]

A concern related to osteoclast-targeting therapies such as zoledronic acid and denosumab is the occurrence of osteonecrosis of the jaw (ONJ), which can be a serious complication.[91] ONJ is a treatment-related adverse event. Although relatively rare, ONJ occurs more frequently (1–10%) in patients with cancer treated with high doses of bisphosphonates or denosumab at monthly intervals for reducing SREs in comparison with individuals treated for indications other than cancer. ONJ is defined as the presence of exposed bone in the maxillofacial region lasting for 8 weeks in patients without prior craniofacial radiation to the jaw, and can lead to treatment interruptions and reduced patient QOL. In the integrated analysis of the three phase III trials mentioned

Table 2 | Physical characteristics of bone-targeting radiopharmaceuticals

Agent	Structure	Emitted radiation	Half-life (days)	Maximum emission energy (MeV)	Standard dose	Mean tissue penetration (mm)
Strontium-89	$^{89}SrCl_2$	β	50.5	1.46	1.48–2.22 MBq/kg	5.5
Samarium-153 lexidronam	^{153}Sm-EDTMP	β and γ	1.9	0.81	37 MBq/kg	2.5
Radium-223	$^{33}RaCl_2$	α	11.4	5.64	0.05–0.25 MBq/kg	<0.1

Abbreviation: EDTMP, ethylene diamine tetramethylene phosphonate.

above, more patients receiving denosumab experienced ONJ compared with zoledronic acid (1.8% versus 1.3%), but the difference was not statistically significant.[92] The treating physician should be aware of strategies to reduce the incidence and consequences of ONJ.[92,93] Risk factors for ONJ include poor oral hygiene, maxillary or mandibular bone surgery, and the use of corticosteroids and antiangiogenic agents. Preventive strategies are encouraged, such as stabilisation of oral disease and the maintenance of good oral hygiene in the patient prior to the use of osteoclast-targeting therapies.[93] Delaying the administration of these agents should be considered for patients undergoing extensive oral surgery until the surgical sites have healed with mature mucosal coverage. Conservative management of ONJ is recommended, including topical antibiotic rinses and systemic antibiotic therapy. Localised surgery has proven successful in patients with advanced unresponsive disease.[93]

Radiopharmaceuticals

^{89}Sr and ^{223}Ra are cationic calcium mimetics that substitute for calcium in inorganic complexes (hydroxyapatite) during mineral formation in areas of increased bone turnover around bone metastases.[24] By contrast, ^{153}Sm is an anionic non-calcium analogue with no natural affinity for bone, but when conjugated with ethylene diamine tetramethylene phosphonate (^{153}Sm lexidronam) it also localizes to bone in association with hydroxyapatite. Once located within the bone matrix, the radiopharmaceuticals have cytotoxic effects on adjacent PCBMs owing to the delivery of focal radiation (Figure 1). The reduction in serum markers of bone metabolism in patients treated with these agents suggests that they might also affect the bone microenvironment.[20,94]

The physical properties of approved radiopharmaceuticals vary (Table 2). Both ^{89}Sr and ^{153}Sm are β-particle-emitting radiopharmaceuticals; ^{153}Sm also emits a small proportion of γ-radiation. Both agents have a relatively far-reaching tissue penetration and low linear energy transfer (LET). LET describes how much energy an ionising particle transfers to the material it is travelling in over the distance it travels and is an indicator of the potential cytotoxicity a radionuclide can cause to tissues—a higher LET leads to potentially more cytotoxicity.[95] However, despite the low LET, the penetration range of β-particle-emissions from ^{89}Sr and ^{153}Sm raises concerns over bone marrow toxicity associated with the use of these agents, particularly with ^{89}Sr, which has a longer half-life than ^{153}Sm. By contrast, ^{223}Ra is an α-particle emitter that has high LET, delivering high energy transfer over a short range. High LET leads to a high frequency of DNA double-strand breaks in adjacent tumour cells, resulting in an enhanced biological effectiveness with a lower chance of bone marrow toxicity compared with β-particle emitters.[24,95]

The β-particle emitter ^{89}Sr

^{89}Sr is widely regarded as obsolete for treating PCBMs; however, discussion of ^{89}Sr provides historical perspective to the development of radiopharmaceuticals and bone-targeting agents for mCRPC. For instance, the results of some small randomized studies suggested an improvement in overall survival in patients treated with ^{89}Sr compared with those in the control arm.[96,97] Although these findings remain controversial, they supported the idea of the close interaction between prostate cancer and bone, and that targeting PCBMs could lead to an improvement in long-term outcome. However, the inherent concerns over toxicity and safety associated with β-particle-emitting pharmaceuticals demanded the development of alternative agents.

Following intravenous injection, ^{89}Sr is rapidly incorporated into bone, with a 5–10-fold greater uptake at sites of metastases compared with normal bone. Unincorporated ^{89}Sr is eliminated through both the urinary (80%) and gastrointestinal systems (20%). ^{89}Sr is approved for the palliation of pain in patients with bone metastases arising from prostate cancer.

A number of randomized studies have evaluated ^{89}Sr in this setting with pain reduction as the primary response criterion.[94,96,98–101] In a systematic review of studies in patients with prostate cancer, complete pain response varied between 8% and 77% (mean 32%), the mean for partial pain response was 44%, mean duration of clinical response was 15 months and reduction of analgesic use was between 71% and 81%.[102] The first randomized, double-blind, multicentre, prospective trial of ^{89}Sr compared this agent with placebo in 126 CRPC patients with bone metastases after receiving local field radiotherapy.[94] Overall survival was longer in patients receiving placebo compared with ^{89}Sr; skeletal outcomes were not reported (Table 1). Pain relief (assessed by a Radiation Therapy Oncology Group analgesic and pain scoring system) at the index site (the site of initial pain) was similar between the treatment groups. By contrast, patients in the ^{89}Sr group had statistically significant improvements in QOL (assessed using a nine category QOL questionnaire) and palliation of pain, decreases in serum PSA and alkaline phosphatase levels (Supplementary Table 1 online).

Another double-blind study in 49 patients with prostate cancer and skeletal metastases found no significant difference in pain relief (primary end point, evaluated using patients' subjective reports) between ^{89}Sr and placebo, although unexpectedly in this small study overall survival at 2 years was higher in the ^{89}Sr arm than in the placebo arm (46% versus 4%).These findings were surprising, as improvements in overall survival had not previously been reported with supportive use of β-particle-emitting radiopharmaceuticals. Skeletal outcomes were not reported.[96]

A phase III trial sponsored by the European Organization for Research and Treatment of Cancer (EORTC), comparing palliative local-field radiotherapy with ^{89}Sr in 203 patients with CRPC and painful bone metastases, showed no significant differences in subjective pain response (assessed using the five-point WHO scale), the duration of pain response in responding patients and in progression-free survival (PFS) between the two treatment arms. Overall survival was longer in patients treated with local-field radiotherapy compared with ^{89}Sr (Table 1).[99]

Re-treatment of painful metastases with radiopharmaceuticals might be required owing to the transient effects of these agents and the progressive course of the disease. The need for re-treatment often indicates a high tumour burden and patients who are more likely to have resistant disease. In one small single-centre study, 118 patients with painful skeletal metastases (predominantly from prostate, lung or breast tumours) were effectively re-treated with ^{89}Sr, without marked myelosuppression, if they had responded well to the first treatment with this agent.[103] In a multicentre, observational study, 81 of 881 patients with prostate cancer and painful bone metastases were re-treated with β-particle-emitting radiopharmaceuticals (including ^{89}Sr). Patients who were re-treated with radionuclides had worse responses than those receiving their first treatment. The authors further reported that those patients who had failed to respond to their first treatment were unlikely to respond to subsequent ^{89}Sr administrations.[104] Comparison of these studies is problematic owing to differences in study designs, the small sample sizes investigated, and the differences in the patient populations studied (prostate tumours versus multiple tumour types). In the absence of further studies, the effectiveness of re-treating patients with ^{89}Sr is inconclusive.

The β-particle emitter ^{153}Sm lexidronam

Following intravenous administration, ^{153}Sm lexidronam localizes to bone with an affinity that is fivefold higher for metastatic sites than for normal bone. The agent is excreted in the urine and clearance from the bloodstream is completed 6 h after injection. Pain relief after ^{153}Sm lexidronam treatment occurs in 60–85% of patients within 1 week of administration, with a clear dose–response correlation in dose escalation studies.[105,106] In 1997, ^{153}Sm lexidronam was approved by the FDA for the relief of pain of cancer that has spread to the bone.

In a phase I study of patients with solid tumours and disseminated skeletal metastases treated with escalating doses (10–36 MBq/kg) of ^{153}Sm lexidronam, pain relief was reported in 65% of patients for periods ranging from 4 weeks to 35 weeks, following a single administration of the drug. The dose-limiting toxic effect was myelosuppression manifested by delayed thrombocytopenia.[107] A double-blind, placebo-controlled phase III study in patients with painful bone metastases secondary to different primary malignancies reported a significant reduction in pain in 62–72% of patients during the first 4 weeks of treatment in the group receiving 37 MBq/kg of ^{153}Sm lexidronam compared with placebo (P <0.016). Reductions in pain score and analgesic use were significantly correlated (P = 0.01).[108] One randomized, controlled phase III study in men with CRPC and bone metastases reported significant improvement in subjective pain response (assessed using a clinical evaluation and global assessment of each patient) in week 2 to week 4 following injection in patients treated with ^{153}Sm lexidronam (37 MBq/kg) compared with those receiving placebo. Reductions in opioid use were observed at week 3 and week 4 (Supplementary Table 1 online).[109] Skeletal outcomes and effects on survival were not reported in this study.

Toxicity of β-particle emitters ^{89}Sr and ^{153}Sm

Haematological toxicity is the most common adverse event associated with ^{89}Sr, although this effect is reversible.[24,25] Leukocyte and platelet nadir counts (reduction range 11–65%) generally occur between 4 weeks to 6 weeks following injection in more than 50% of patients, with recovery by week 12. A flare phenomenon, a transitory increase in bone pain early in the course of treatment, occurs in 15% of ^{89}Sr-treated patients.[24]

Marrow toxicity is the principal adverse effect of ^{153}Sm lexidronam.[108,109] Leukocyte and platelet counts decrease between 3 weeks and 6 weeks, but generally recover by week 8.[107,109] Across three randomized trials using a single administration of ^{153}Sm, the incidence of thrombocytopenia and neutropenia equal or greater than grade 3 was 3–15% and 5–14%, respectively.[108–110] At standard doses (18.5–37 MBq/kg), mean reductions in platelet counts were 43–45% and mean declines in white blood cell counts ranged from 49% to 51%.[108,110]

Clinical utility of ^{89}Sr and ^{153}Sm

In summary, ^{89}Sr and ^{153}Sm are approved for the treatment of bone pain in patients with cancer and painful skeletal metastases and bone pain from unresectable osteosarcoma. In prostate cancer, although the findings are not universal, both ^{89}Sr and ^{153}Sm seem to exert clinically relevant analgesic effects in patients with painful bone metastases from CRPC, but have not been convincingly shown to decrease the frequency of SREs or to prolong survival.

The haematological toxicity associated with β-particle-emitting radiopharmaceuticals requires the regular haematological monitoring of patients, including measurement of baseline blood cell counts prior

to first administration and regular monitoring (every week for 8 weeks) following administration; treatment-free intervals can also be necessary. Thus, the associated haematological toxicity not only limits the use of β-particle-emitting agents as therapeutics, but can also compromise the administration of subsequent chemotherapy, which has an increasingly important role in the management of patients with advanced CRPC, but also often causes haematological toxicity.[12,13] Other contraindications to the use of β-particle-emitting radiopharmaceuticals include radiotherapy within the previous 2 months, impending cord compression or pathological fracture, renal insufficiency, Karnofsky performance status <50% and disseminated intravascular coagulation.[25,111]

The α-particle emitter ^{223}Ra

Animal studies demonstrated the preferential uptake of ^{223}Ra in osteoblastic lesions compared with normal bone, and the short path length of this α-particle-emitting compound.[95] In clinical studies, the total skeletal uptake of ^{223}Ra in patients was approximately 40–60% of the administered dose.[24,95] A dosimetry study after intravenous injection of ^{223}Ra, showed that bone endosteum and red bone marrow contained the highest dose equivalents, followed by liver, colon and intestine.[112] Approximately 4% of the injected radioactivity remained in blood 4 h after injection and the majority of the remaining activity was found in the bone and intestine. A large proportion (63%) of ^{223}Ra is excreted from the body within 7 days of injection. The main route of excretion is faecal, with the median cumulative faecal and urine excretions within 48 hours after injection being 13% (range 0–34%) and 2% (range 1–5%), respectively.[113,114]

Efficacy and safety of ^{223}Ra

Early clinical studies demonstrated that ^{223}Ra has a favourable safety profile with minimal myelotoxicity.[115,116] Phase II studies showed that ^{223}Ra reduces pain and improves levels of disease-related biomarkers BALP and PSA.[116–118] In addition, one of the trials suggested an overall survival benefit compared with placebo (65.3 weeks versus 46.4 weeks; HR 2.12, 95% CI 1.13–3.98, $P = 0.020$) in patients with CRPC and bone metastases.[116] This new finding of a potential survival benefit from the use of a bone-targeted radiopharmaceutical in this setting required that the results from the phase II study were independently verified in a randomized phase III trial.

The pivotal phase III ALSYMPCA trial was a randomized, double-blind, placebo-controlled trial of ^{223}Ra in 921 patients with symptomatic CRPC and two or more bone metastases (men with visceral metastases were excluded).[20] Patients were eligible regardless of whether they had previously received docetaxel. Patients were randomly assigned (2:1) to receive six injections of ^{223}Ra (50 kBq/kg) or placebo every 4 weeks. Baseline characteristics were generally balanced between the two groups. In an interim analysis of overall survival (primary end point) involving 809 patients that was performed after 314 deaths had occurred, a 30% reduction in the risk of death was reported in patients treated with ^{223}Ra compared with placebo. The survival benefit was maintained in an updated analysis following 528 deaths occurring in all recruited patients (Table 1). In subgroup analyses, the benefit of ^{223}Ra over placebo for overall survival was evident in patients previously treated with docetaxel (14.4 versus 11.3 months; HR 0.70, 95% CI 0.56–0.88) as well as those who did not receive prior docetaxel (16.1 versus 11.5 months; HR 0.69, 95% CI 0.52–0.92).[20,119]

The effects of ^{223}Ra on SSEs (secondary end point) in the ALSYMPCA study were also reported (Table 1 and Supplementary Table 1 online).[26] The most commonly detected individual SSE component in the intention-to-treat population (921 patients) was the need for EBRT for bone pain (291 patients, 32%). Symptomatic pathological bone fracture occurred in 52 patients (6%), spinal cord compression in 46 patients (5%) and tumour-related orthopaedic surgical intervention was performed in 19 patients (2%). Time to first SSE was longer and the risks of EBRT for bone pain and spinal cord compression were reduced in the ^{223}Ra group compared with the placebo group. However, ^{223}Ra treatment did not significantly reduce the risk of symptomatic pathological bone fracture or the need for tumour-related orthopaedic surgical intervention, but these events are relatively rare in mCRPC.[26]

In a *post hoc* analysis of pain parameters, in addition to reduced risk of EBRT for bone pain, fewer patients in the ^{223}Ra group than in the placebo group reported bone pain as an adverse event (50% versus 62%).[27] In patients with no opioid use at baseline, those in the ^{223}Ra group experienced a significantly longer median time to initial opioid use with a risk reduction of 38% compared with patients in the placebo group (HR 0.621, 95% CI 0.456–0.846). In addition, fewer patients in the radiopharmaceutical group than in the placebo group required opioid use for pain relief (36% versus 50%). Regarding other secondary end points in the ALSYMPCA study, time to increase in the total alkaline phosphatase level and time to increase in PSA levels were longer for patients in the ^{223}Ra arm compared with those in the placebo arm.[20] A significantly higher percentage of patients who received ^{223}Ra compared with those who received placebo (25% versus 16%; $P = 0.002$) had a meaningful improvement in QOL according to the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score during the period of drug administration (Supplementary Table 1 online).

Safety in the ALSYMPCA study was assessed in 600 patients receiving at least one dose of ^{223}Ra and 301 patients receiving placebo.[20] Safety profiles were similar between the treatment arms; no clinically meaningful differences were reported in the frequency of any grade, or grade 3 or grade 4 adverse events between the treatment groups. Grade 3 febrile neutropenia was reported in one patient (<1%) in the ^{223}Ra group and in one patient (<1%) in the placebo group. Only one

grade 5 haematological adverse event was considered to be possibly related to ^{223}Ra. However, ^{223}Ra has the potential for haematological toxicity with about 2% of patients in the ^{223}Ra arm experiencing bone marrow toxicity and pancytopenia. Consequently, measurement of haematological parameters is required before first administration and before every subsequent dose of ^{223}Ra; before first administration, patient absolute neutrophil count should be $\geq 1.5 \times 10^9$/l, haemoglobin ≥10 g/dl and platelet count should be $\geq 100 \times 10^9$/l.[113,120] Pregnant patients should not receive ^{223}Ra. No other specific contraindications for use of ^{223}Ra have been reported.[113] Based on these results, ^{223}Ra has been approved by the FDA and EMA for the treatment of patients with CRPC and evidence of bone metastases but no known visceral disease.

In summary, historically, bone-targeting agents, in particular β-particle-emitting radiopharmaceuticals, were largely viewed as suitable for the supportive care of CRPC patients with bone metastases. Consequently, initial trials focused mainly on the alleviation of pain as a primary clinical end point and more recently in the case of osteoclast inhibitors (zoledronic acid and denosumab) for the prevention of SREs or SSEs. Compared with these agents, ^{223}Ra is the first bone-targeting agent to extend overall survival and reduce SSEs. Thus, ^{223}Ra could be considered as a bone-targeting agent with disease-modifying properties. A number of active and ongoing clinical studies are further investigating the safety of ^{223}Ra, and its use in combination with chemotherapy (specifically docetaxel)[121] and with the new antiandrogens abiraterone and enzalutamide.[122–124] The details of investigated treatments and specified primary outcomes in these studies are listed in Supplementary Table 2 online.

Systemic agents and skeletal outcome

Several systemic disease-modifying agents also have effects on skeletal outcomes and overall survival in patients with mCRPC (Table 1). A detailed summary of the efficacy of these agents in this setting is provided in Supplementary Table 3 online.

Cytotoxic chemotherapy

The taxanes docetaxel and cabazitaxel are approved for the treatment of patients with mCRPC and bone metastases. In the randomized, nonblinded phase III trial TAX 327, patients given daily prednisone and either weekly or 3-weekly docetaxel had longer overall survival (Table 1), and also experienced reductions in serum PSA levels, pain (assessed with the present pain intensity [PPI] scale from the McGill–Melzack questionnaire) and improvements in QOL (assessed with the FACT-P questionnaire) compared with those receiving prednisone and 3-weekly mitoxantrone.[12] In the randomized, open-label phase III TROPIC trial, adding cabazitaxel to prednisone significantly improved overall survival in patients with mCRPC compared with those receiving prednisone plus mitoxantrone (median 15.1 months versus 12.7 months; HR 0.70, 95% CI 0.59–0.83, $P < 0.0001$).[13] Patients receiving cabazitaxel also had longer study-specific PFS (defined as a composite of PSA progression, tumour progression, pain progression or death), however palliation of pain (assessed using the PPI scale) was similar between the groups. Neither the TAX 327 nor the TROPIC study reported SREs as an end point. In the ASCENT study in patients with androgen-independent prostate cancer, a trend towards increased SRE-free survival (planned secondary end point) was reported in men receiving docetaxel-based therapy (Table 1).[125] None of these studies reported investigations of markers of bone turnover.

Biologically targeted therapies

The endothelin A receptor on bone sensory nerve endings and ET-1 are potentially prime targets for therapeutic intervention in mCRPC, although data from randomized phase III trials with endothelin A receptor antagonists atrasentan and zibotentan were disappointing in this setting. In a double-blind phase III trial in patients with mCRPC, single-agent atrasentan compared with placebo showed no improvement in the primary end point, time to tumour progression (radiological and clinical, including SREs), or secondary end points, including overall survival and time to PSA progression.[126] In exploratory analyses, increases from baseline to final BALP and PSA levels were significantly lower with atrasentan treatment compared with placebo ($P < 0.05$), and atrasentan significantly prolonged the time to increase in BALP levels in comparison with placebo (505 days versus 254 days; HR 0.56, 95% CI 0.42–0.75).[126] A randomized phase III study of zibotentan in men with mCRPC and bone metastases showed no difference of this agent compared with placebo in the primary end point overall survival, or reported secondary end points including PFS (radiological and clinical, including SREs), time to pain progression (pain assessed using the Brief Pain Inventory [BPI]), time to opiate use, time to PSA progression, and QOL (assessed using the FACT-P questionnaire).[127] Combination of docetaxel with either atrasentan[128] or zibotentan[129] also failed to improve long-term outcomes compared with chemotherapy plus placebo in this setting.

The Src family are non-receptor tyrosine kinases that regulate a wide range of cellular activities including osteoclastic activity, tumour growth and metastasis.[130] High levels of the proto-oncogene tyrosine-protein kinase Src are found in mature osteoclasts and Src activity is essential for bone remodelling through both the positive and negative regulation of osteoclasts and osteoblasts, respectively. Evidence exists that Src has a role in mediating prostate cancer development and metastasis to the bone.[130] Dasatinib is a tyrosine kinase inhibitor of Src activity. Phase I and phase II studies in patients with mCRPC of dasatinib alone[131–133] or in combination with docetaxel[134] demonstrated encouraging results including control of disease progression and bone activity (assessed by measurement of markers of bone turnover; uNTx and BALP). In the multinational, randomized, double-blind, placebo-controlled

phase III trial READY in men with mCRPC, adding dasatinib to docetaxel did not improve overall survival (21.5 months versus 21.2 months; HR 0.99, 95.5% CI 0.87–1.13). No differences were observed in most of the secondary end points including reduction in uNTx levels, although an increase in median time to first SRE was reported in the dasatinib arm (median not reached versus 31.1 months; HR 0.81, 95% CI 0.64–1.02).[135] Other Src inhibitors (saracatinib, KX2-391 and bosutinib) are in development.[65]

Hepatocyte growth factor receptor (encoded by *MET*), a receptor tyrosine kinase, its ligand hepatocyte growth factor and the vascular endothelial growth factor signalling pathway are all implicated in the development and progression of CRPC.[136] Cabozantinib is a novel receptor tyrosine kinase inhibitor of the hepatocyte growth factor receptor and VEGFR-2 and demonstrated both direct antitumour activity and the ability to modulate osteoblast activity in human prostate cancer xenograft models in mice.[137] In a randomized phase II discontinuation trial, patients with mCRPC and stable disease following 12 weeks of daily treatment with cabozantinib were randomized to cabozantinib or placebo.[136] The study enrolled 171 men; of 116 evaluable patients, with PCBMs at baseline and at least one follow-up bone scan, 68% demonstrated a response in their bone metastases on bone scan, including complete resolution in 12% of patients. The objective response rate at week 12 was 5%, with stable disease measured in 75% of patients. Following randomization, PFS was significantly longer in patients receiving cabozantinib compared with placebo (23.9 weeks versus 5.9 weeks; HR 0.12, $P<0.001$). In 57% of evaluable patients, serum total alkaline phosphatase levels and plasma cross-linked C-terminal telopeptide of type I collagen levels were reduced by ≥50%. On retrospective review, bone pain improved in 67% of evaluable patients, with a decrease in the use of narcotics in 56%. In September 2014, data were released from the randomized phase III study COMET-1 of cabozantinib in men with mCRPC.[138,139] The study did not meet the primary end point of a statistically significant difference in overall survival in patients treated with cabozantinib compared with prednisone (median 11.0 months versus 9.8 months; HR 0.90, 95% CI 0.76–1.06). Data for an exploratory end point PFS (investigator-assessed) were also available: median PFS was 5.5 months for patients in the cabozantinib arm compared with 2.8 months for the prednisone arm (HR 0.50, 95% CI 0.42–0.60, $P<0.001$). Owing to these results, enrolment in the COMET-2 study (primary end point pain reduction) has been halted and the study terminated.[140]

Hormone-based therapies

Reactivation of androgen receptor (AR) signalling occurs in the progression of prostate cancers to CRPC, caused by a variety of mechanisms, including the upregulation of androgen biosynthesis enzymes or overactivation of ARs in prostate tumours.[141] Thus, CRPC tumours remain androgen-dependent on progression. Importantly, the AR is also expressed on stromal cells in the bone microenvironment, and AR signalling also promotes tumour growth through its activity in stromal cells.[142,143] Abiraterone is an inhibitor of steroid 17-α-hydroxylase/17,20 lyase, a critical enzyme in testosterone biosynthesis, and blocks testosterone synthesis in the adrenal glands, testes and the tumour.[144] Abiraterone is approved for use in patients with mCRPC either before or following chemotherapy.[15–17]

The double-blind, placebo-controlled, randomized phase III trial COU-AA-301 in patients with mCRPC previously treated with docetaxel, demonstrated a significant improvement in overall survival on adding abiraterone to prednisone compared with placebo ($P<0.001$; Table 1).[15] The median overall survival benefit was extended to 4.6 months in an updated analysis.[16] In addition, a significant reduction in time to first SRE ($P=0.0001$; Table 1) and effective pain palliation (assessed by BPI–Short Form [BPI-SF] and analgesic use) were reported in exploratory analyses of prospectively collected data (Supplementary Table 3 online).[145] In the randomized, double-blind, placebo-controlled phase III study COU-AA-302, the combination of abiraterone with prednisone compared with prednisone alone in chemotherapy-naive patients with mCRPC significantly improved overall survival ($P=0.01$; Table 1) and PFS (co-primary end points) and demonstrated a marked improvement in secondary end points, including time to initiation of cytotoxic chemotherapy, PSA progression and palliation of cancer-related pain (assessed by BPI-SF) and QOL (assessed by FACT-P questionnaire).[17,146] In this study, SREs were not reported. A prespecified final analysis of overall survival, after a follow-up period of >4 years, confirmed the survival benefit in patients receiving abiraterone compared with placebo (median 34.7 months versus 30.3 months; HR 0.81, 95% CI 0.70–0.93, $P=0.0033$).[147]

The antiandrogen enzalutamide inhibits the AR, affecting its nuclear translocation, DNA-binding and co-activator recruitment, and is currently approved for patients with mCRPC progressing on docetaxel.[148] The randomized phase III trial AFFIRM showed a significant improvement in overall survival ($P<0.001$) and delay in the time to first SRE ($P<0.001$) in men with CRPC who received enzalutamide in comparison with placebo (Table 1).[18,19] In a prospectively designed analysis of some of the AFFIRM secondary end points, enzalutamide was superior to placebo in all end points analysed, including the proportion of patients with reduction in PSA levels of ≥50% and time to PSA progression, as well as parameters of pain palliation (assessed with BPI-SF, a diary of pain, narcotic analgesic use, and the FACT-P questionnaire) and QOL (according to FACT-P questionnaire); data presented in Supplementary Table 3 online.[19] The double-blind, multinational, randomized phase III trial PREVAIL of enzalutamide compared with placebo in patients with CRPC who had not received prior chemotherapy showed enzalutamide to significantly improve overall survival ($P<0.001$; co-primary end point) and prolong

time to first SRE (P <0.001; Table 1). A beneficial effect in PFS (co-primary end point) and PSA progression (secondary end point) and in prespecified exploratory analyses for a decline in QOL (by FACT-P questionnaire) and in pain progression (by BPI-SF) was also demonstrated in enzalutamide-treated patients.[149,150]

In summary, most randomized studies of chemotherapy show an improvement in overall survival in men with CPRC, but have not examined skeletal outcome as an end point. New hormone-based treatments with abiraterone or enzalutamide improve survival and skeletal outcome—at least time to first SRE—in this setting. None of the reviewed studies reported on markers of bone turnover as an end point. Cabozantinib, an agent targeting both tumour cells and the bone microenvironment has shown efficacy in men with mCRPC in early clinical studies and is under further clinical development.

Treatment options for PCBMs

EBRT and bone-targeting radiopharmaceuticals are important in alleviating the pain associated with bone metastases in patients with mCRPC.[2,3,94,98,109] In addition, the osteoclast-targeting agents zoledronic acid[21,22] and denosumab[23] are key in reducing skeletal-related morbidity and improving QOL, which are associated with long-term outcome in this setting.[34,35] Clinical guidelines recommend initiating zoledronic acid or denosumab treatment in all patients with mCRPC and bone metastases. However, consensus over the optimal duration of treatment is lacking.[59]

To address the issue of optimal duration of treatment more personalised patient data are required, accounting for response to antineoplastic treatment, number and location of bone metastases, bone pain, performance status, and levels of bone markers (BALP and uNTX). Biomarkers of bone metabolism (BALP, uNTX) generally reflect rates of overall ongoing bone resorption or turnover and are not specific to individual lesions. Changes in bone marker levels are also not necessarily disease-specific, but are associated with alterations in skeletal metabolism independent of underlying causes.[59] However, bone biomarkers might be useful in identifying patients at high risk for bone metastasis or progression of their bone lesions and, therefore, might aid in directing future treatment.[59,151]

The prognostic and predictive value of biomarkers of bone metabolism was investigated in patients with mCRPC and skeletal metastases in the SWOG 0421 study.[152] Elevated baseline levels of uNTX, serum C-terminal type 1 collagen propeptide and BALP were associated with worse survival (P <0.001). Patients with the highest marker levels (upper 25th percentile for all markers) not only had poor prognosis (HR 4.3; P <0.01), but also demonstrated a survival benefit from treatment with the ET-1 antagonist atrasentan compared with placebo (median 13 months versus 5 months; HR 0.33, P = 0.005). However, data from ongoing clinical trials are required to evaluate the value of markers of bone metabolism in clinical practice.[59]

For improving overall survival, docetaxel is a standard of care for patients progressing with mCRPC. However, not all can tolerate the treatment; many patients with CRPC might not be healthy enough to receive docetaxel, owing to poor performance status and/or comorbidities, or they decline treatment.[11,12,153] Furthermore, data presented in 2014 suggest that for some patients with metastatic hormone-sensitive prostate cancer treatment with docetaxel should be considered as a first-line option together with castration.[154] Other systemic disease-modifying agents are available in this setting, including cabazitaxel,[13] novel hormone-based therapies (abiraterone and enzalutamide)[15–19,149] and immunotherapy (sipuleucel-T).[14] Among bone-targeting agents, ^{223}Ra is currently the only agent suitable for improving overall survival in patients with mCRPC and bone metastases.

Prospective data addressing optimal treatment combinations and sequencing in CRPC are not available and head-to-head comparisons of novel therapeutics have not been performed. However, based on the current treatment paradigm, three positions for novel agents seem to exist in the treatment schedule of patients with CRPC: before docetaxel, in combination with docetaxel or after docetaxel.[155,156] Sipuleucel-T is preferred in chemotherapy-naive patients and abiraterone and enzalutamide are active both before and after docetaxel treatment.[14,17,149] Currently cabazitaxel is approved for patients progressing on or after docetaxel treatment.[13]

For ^{223}Ra, several positions in the treatment paradigm seem suitable. In the ALSYMPCA trial, the survival and toxicity profiles of patients receiving ^{223}Ra either before or after docetaxel were similar.[119] The consensus in Europe is for ^{223}Ra to be used either before or, alternatively, after docetaxel.[20,119,153]

Evidence also exists that bone-targeting agents might be useful earlier in the treatment paradigm. In patients with CRPC and high risk of bone metastases, denosumab significantly increased bone-metastases-free survival (HR 0.85, 95% CI 0.73–0.98, P = 0.028) and delayed time to first symptomatic bone metastasis (HR 0.84, 95% CI 0.71–0.98, P = 0.032) compared with placebo; however, overall survival was similar between the groups.[157] An exploratory sensitivity analysis of the data reported a larger effect of denosumab when the PSA doubling time was short, but denosumab is not approved in this indication.[158] By contrast, zoledronic acid was not effective in the ZEUS study in patients with high-risk nonmetastatic prostate cancer.[76] ^{223}Ra has not yet been investigated in this treatment setting. Furthermore, its use might be limited unless repeat treatment cycles can be given. For example, in the absence of the bone turnover that is usually induced by bone metastases, ^{223}Ra might not be incorporated into the bone and, thus, would be ineffective.

For combination therapy in the treatment of bone metastases in patients with mCRPC, with respect to improving long-term outcomes, combinations of systemic agents, including dasatinib, atrasentan, or zibotentan with docetaxel, have generally been disappointing,

possibly owing to the modest clinical activity reported for each as a single agent.[128,129,134] For bone-targeting agents, some studies have demonstrated encouraging data from the combination of radiopharmaceuticals with docetaxel with respect to clinical pain response.[24,97] Preclinical data suggest that zoledronic acid might enhance the antitumour activity of cytotoxic agents.[69] In the TRAPEZE trial in patients with mCRPC and bone metastases, the addition of zoledronic acid to docetaxel was beneficial for prevention of SREs, but this combination did not improve survival.[159]

An ongoing phase I/IIa trial is investigating ^{223}Ra in combination with docetaxel in men with CRPC and bone metastases.[121] In the dose escalation part of the study (phase I), the treatment combination was overall tolerable, and a regimen of 3-weekly docetaxel (60 mg/m^2) in combination with 6-weekly ^{223}Ra (50 kBq/kg) versus docetaxel (75 mg/m^2) alone was investigated in an expanded safety cohort in the randomized phase IIa part of the trial.[160] Combination of ^{223}Ra with bone-targeting agents such as zoledronic and denosumab might also have potential, whereby the effects on reducing skeletal morbidity could be enhanced owing to the different modes of action of these agents, and the combination might be tolerated owing to non-overlapping toxicity profiles (^{223}Ra is not associated with hypocalcaemia or renal toxicity). Combinations of bone-targeting agents with novel hormone-based therapies are also under investigation. In 2013, a *post hoc* analysis of data from the COU-AA-302 study in chemotherapy-naive patients demonstrated that, in patients with bone metastases at baseline, treatment with bone-targeting agents (including zoledronic acid and other bisphosphonates, denosumab, and/or other bone-targeting agents) in combination with abiraterone was associated with significantly improved outcomes, including overall survival (HR 0.754, $P = 0.012$), time to opiate use (HR 0.801, $P = 0.036$), time to ECOG performance status deterioration (HR 0.750, $P < 0.001$), compared with those not receiving this combination.[161] Clinical investigations of the combination of ^{223}Ra with new hormone-based therapies (abiraterone or enzalutamide) are ongoing (Supplementary Table 2 online).[122–124]

Discussion and future perspectives

Historically, the treatment of bone metastases in mCRPC has largely been supportive and centred around the management of pain through localized radiation therapy or targeting the bone microenvironment with β-particle-emitting radiopharmaceuticals.[94,99,109] In the past 15 years, reduction in SREs using osteoclast inhibitors has been demonstrated with bisphosphonates, such as zoledronic acid, and more effectively with denosumab.[21–23] However, improvements in long-term outcome for these patients were realistically only achievable with cytotoxic chemotherapy, specifically docetaxel.[11,12]

Data from studies in the past decade demonstrate that targeting both the proliferating tumour cells and the bone microenvironment is an effective strategy for improving long-term outcome, including survival. For example, single-agent ^{223}Ra significantly improved overall survival and reduced SSEs in patients with CRPC and bone metastases.[20,26] Data from preclinical studies suggest that, in addition to inhibiting osteoclast activity, both zoledronic acid and denosumab have the potential to target prostate cancer metastases.[69] However, to date, neither agent has demonstrated an improvement in overall survival in the clinical setting. New hormone-based therapies abiraterone[15–17] and enzalutamide[18,19] delay SREs and prolong overall survival, although the randomized studies did not elucidate whether these effects are caused through control of the metastatic cells, effects on bone microenvironment or both. Similarly, most studies with docetaxel[11,12] and cabazitaxel[13] did not include SREs or markers of bone turnover as end points, so the contribution of these agents to improving skeletal outcome is difficult to assess.

As we understand more about the pathophysiology of CRPC bone metastasis and identify potentially better agents to treat patients, we can improve the design of clinical trials to assess their efficacy. However, the high complexity in how the multiple cell types interact with each other over time represents a major challenge to determining the effects of specific growth factors and/or cytokines or, indeed, targeted therapies in the progression of prostate cancer to the metastatic stage. In addition, comparisons between trials prove problematic when trying to assess the potential effectiveness of a drug or drug combinations, because many studies have, over time, used different end points and different methodologies for assessing those end points.

The advent of the integration of computer modelling with biological models of mCRPC might aid in solving these problems. First, in the preclinical setting, these new approaches might enable the investigation of the complex interactions between different cells, proteins and drugs to delineate the importance of individual molecular pathways. Second, the integration of computer models with individual patient-derived biological data might serve as a potential surrogate to costly and time-consuming clinical trials in an attempt to optimize therapy choice and sequence.[62,162,163]

Conclusions

Bone is often the first site for metastasis and bone metastases develop in the majority of patients with mCRPC. Bone metastases are associated with increased skeletal morbidity and reduced overall survival of patients with CRPC.[5–9] Advances in our understanding of prostate tumour biology have revealed that the growth of bone metastases involves the interaction between proliferating tumour cells and cells that naturally exist within the bone microenvironment. Elucidation of the molecular mechanisms underlying these cellular interactions has identified potential targets for the development of therapeutic interventions in this disease, highlighted by the approval of the bone-targeting agents denosumab[23] and ^{223}Ra,[20,26] and has led to early and ongoing clinical investigations of cabozantinib.[136,139,140]

In the meantime, ongoing clinical studies are investigating combinations of approved agents and their optimal position in the current treatment paradigm to improve clinical outcomes of patients with mCRPC. The regular inclusion of SREs and/or SSEs and biomarkers of bone turnover as end points in future trials might aid in characterizing further the cellular targets and the efficacy of new agents. In addition, further understanding of the pathophysiology of bone metastases in mCRPC might lead to the identification of more effective treatments for patients with this disease.

Review criteria

The PubMed data base was searched for articles written in English without restriction on publication date. American Society of Clinical Oncology abstracts were searched with a time limit from 2010–2014. Search terms in various combinations included: "metastatic castration-resistant prostate cancer", "bone metastases", "chemotherapy", "docetaxel", "cabazitaxel", "radiopharmaceuticals", "radium 223", "strontium 89", "samarium 153", "hormone therapy", "abiraterone", "enzalutamide", "survival", "skeletal events".

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