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Prostate cancer metastases to bone: Pathophysiology, pain management, and the promise of targeted therapy

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Abstract

Bone metastases are a significant cause of pain and morbidity in prostate cancer, especially if they lead to complications such as pathological fractures and spinal cord compression. Palliation of pain can be achieved with radiation, radioisotopes, hormone therapy, chemotherapy, and bisphosphonates. Bisphosphonates also reduce the risk of skeletal complications. Studies with animal models and advances in understanding the molecular basis for bone metastases have yielded new targets for therapy. Some of the promising therapeutic trials are reviewed in this paper.

Keywords: Prostate cancer; Bone; Metastases; Pain; Targed therapy; Palliation

1. Introduction

Metastases to bone are a common and morbid complication of prostate cancer: 85% of men who die of prostate cancer have bone metastases [1]. Pain management often becomes a primary focus of treatment, and therapy is designed to prevent disability from cord compression and fractures as much as it is aimed at prolonging survival. While chemotherapy and bone-specific treatments (i.e. radioisotopes, bisphosphonates) have improved for metastatic prostate cancer, advanced understanding of the molecular mechanisms by which tumour cells flourish in bone provides hopeful ground for even more effective therapies in the future, and opportunities for prevention.

2. Pathophysiology

Stephen Paget first proposed the concept of "seed" and "soil" in 1889 to explain why different types of tumour cells favour particular sites for metastasis [2]. Since that time, elucidation of some molecular mechanisms involved in tumour metastasis to bone have supported and expanded on his hypothesis. Not only is there a high volume of blood flow through bone marrow, offering tumour cells ample access to bone, but the flow direction fluxes with intrathoracic and abdominal pressure changes, providing opportunity for adhesion [3]. In order to settle in bone tissue, prostate cancer cells express adhesion molecules with affinity for bone. One example is $\alpha 2\beta a1$ integrin, which interacts with bone matrix type I collagen [4]. Once attached, tumour cell growth is promoted by local growth factors, which exist in high concentrations due to their release during bone resorption. These stimulatory cytokines include transforming growth factor β (TGFβ), insulin-like growth factors (IGF) I&II, fibroblast growth factors (FGF), platelet-derived growth factors (PDGF), bone morphogenic proteins (BMP), and endothelin-1 (ET-1) [5,6].

Matrix metalloproteinases (MMPs) were originally suspected of facilitating the breach of the basement membrane, which theoretically allowed tumour cells to

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escape from their primary location and metastasis. With the capacity to digest a wide variety of proteins, receptors, and extracellular matrix substrates, MMPs are now understood to participate more broadly, remodelling the metastatic environment to facilitate tumour colonisation [7]. Normal tissues express low levels of MMPs, and have counteracting inhibitors called tissue inhibitors of metalloproteinases (TIMPs). Elevated levels of MMPs have been noted in tumour tissue, as well as any tissue with inflammation or healing [8]. In animal models of melanoma, overexpression of TIMPs resulted in delayed development and suppressed growth of metastases [9,10]. Further data are needed specifically for prostate cancer and bone metastases, but these active proteins are likely to play a major role.

Normal bone remodelling is a balance between resorption by osteoclasts and new bone formation by osteoblasts; dysfunction of either action leads to compromise of bone structure and integrity. Osteoblastic bone metastases, which are the predominant lesions in prostate cancer, result from disordered proliferation of osteoblasts with incomplete bone calcification [11]. A number of receptors and cytokines that take part in this disordered proliferation have been delineated. First, TGFβ, which is present from bone resorption, stimulates upregulation of α2β1 integrin on tumour cells, facilitating their anchoring to type I collagen in the bone matrix [12] (Fig. 1). Second, human prostate cancer cells produce urokinase-type plasminogen activator (u-PA), which stimulates osteoblast mitogenesis either directly, or perhaps by activating TGF-β [4,13]. Work with animal models has confirmed the significance of uPA in the development of bone metastases (see below). Third, prostate cancer cells secrete bone morphogenetic proteins (BMPs), which recruit osteoblast precursors and activate the promoter for vascular endothelial growth factor (VEGF). VEGF itself stimulates osteoblast migration and differentiation, amplifying the signal [14]. Finally, prostate cancer cells express endothelin and its receptors [15]. Endothelin-1 (ET-1) promotes

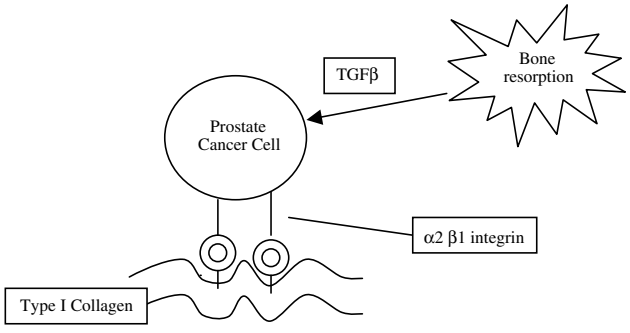

Fig. 1. Presence of TGFβ as a product of bone resorption promotes adhesion of prostate cancer cells to the bone matrix via up-regulation of α2β1 integrin.

proliferation of osteoblasts and enhances the stimulatory effect of BMPs, IGF-I&II, PDGF, EGF, and FGF.

Endothelin-1 has become a focus of interest in hormone-refractory prostate cancer (HRPC) because prostate cancer cells, from both primary and metastatic tumours, have been shown to express ET-1, and because patients with metastatic disease have elevated plasma ET-1 concentrations [16]. In normal bone, ET-1 promotes osteoblast DNA synthesis and phosphate preparation for matrix mineralisation [17]. In vitro, ET-1 has been shown to stimulate the growth of prostate cancer cell lines and enhance their growth response to IGF and PDGF stimuli. This effect is inhibited by blockade of the ET-1 receptor A [16]. Thus, by secreting ET-1, prostate cancer cells may promote their own growth directly, as well as indirectly via stimulation of osteoblasts, which produce factors that further promote tumour growth (Fig. 2). At the same time, since osteoblast proliferation and matrix mineralisation are stimulated, osteoblastic changes result. Interrupting this signal pathway holds therapeutic promise; in animal models blockade of the ET-1 receptor prevented the development of bone metastases [15,18].

There is some anatomical and biochemical evidence to suggest that metastatic prostate cancer cells also stimulate osteoclasts. Autopsy studies have revealed areas of osteolytic histology [19]. Interleukin-6 (IL-6), a cytokine known to activate osteoclasts [20], is elevated in the serum of prostate cancer patients with bone metastases [21]. Urinary excretion of the *n*-terminal telopeptide of type I collagen, free deoxypyrridinoline, and hydroxyproline were all found to be elevated in prostate cancer patients with bone metastases, even more than similar breast cancer patients, whose bone metastases were predominantly osteolytic [22]. Pyridinoline, a serum marker of bone destruction and turnover, is often elevated in metastatic HRPC, and was shown to correlate more directly with the burden of bone disease than serum alkaline phosphatase, a marker of osteoblast activity [1]. Prostate cancer cells have also been shown to consistently express parathyroid hormone-related protein (PTHrP) [23], a factor known to stimulate osteoclast activity. Cleavage of PTHrP by prostate-specific antigen (PSA) may ameliorate its hypercalcaemic effects and limit the osteoclastic component of prostate cancer metastases to bone [24]. In summary, it is likely that prostate cancer cells harness both osteoclasts and osteoblasts in order to flourish in the bone environment.

IL-1, IL-6, IL-11, and PTHrP are thought to mediate their induction of osteoclast proliferation by triggering the receptor activator of nuclear factor-κB ligand (RANKL)-RANK interactions [25]. Interestingly, RANKL was also shown to be produced by osteomimetic prostate cancer cell lines that have the propensity for homing to bone [26]. As the common final pathway, this is a molecular target with great therapeutic potential.

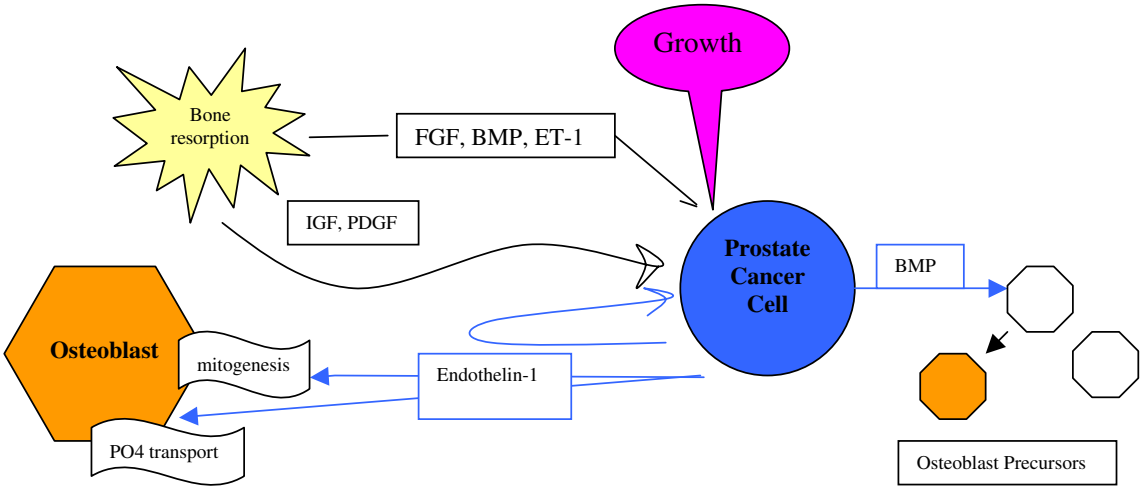

Fig. 2. Signalling between prostate cancer cells and osteoblasts promotes growth of cancer, plus osteoblast differentiation, proliferation, and matrix mineralization.

Monoclonal antibodies to RANKL are under development; initial studies in mice show that RANKL blockade prevents the hypercalcaemia associated with human xenograft growth [26]. An alternative strategy is to use an analogue of osteoprotegerin (a decoy RANK receptor), which also binds to the RANK ligand, preventing it from stimulating osteoclasts.

3. Animal models of prostate cancer bone metastases

The interactions between certain cells, which are part of prostate cancer bone metastasis microenvironment, and prostate cancer cells and osteoblasts, can be evaluated in a co-culture system in vitro [27]. A more complete picture of the interactions between the various cell types involved in prostate cancer bone metastasis can be obtained by studying animal models of bone metastasis. However, the study of prostate cancer bone metastases in vivo has been challenging. Spontaneous prostate cancers are far less common in dogs than in humans, and even more rare in mice [28]. Lobund Wistar rats have an unusual predisposition to prostate cancer. However their tumours, even after progression from androgen dependence to independence, metastasis to lymph nodes and the lungs rather than bone [28]. Prostate (and seminal vesicle) adenocarcinomas were induced in approximately 40% of a group of Noble rats, using testosterone implants in combination with intravenous methylnitrosurea [29]. The natural history of these tumours is unclear; animals were sacrificed as soon as tumours were palpable so that site of origin could be determined.

Rat prostate cancer cell lines have been developed, specifically Mat LyLu. When injected into the left ventricle of Copenhagen rats, animals reliably develop hind limb paralysis (a clinical marker of bone metastasis) within 20–21 days [30]. This model has been used to confirm the in vivo significance of some of the molecular interactions mentioned earlier. For example, when Mat LyLu tumour cells were modified by viral transfection to overexpresses uPA, hind limb paralysis developed in 14–15 days, whereas tumour cells that underexpressed uPA did not generate paralysis by day 27 [31].

Nude mice are probably the best available model in which to study prostate cancer biology and therapy. Both PC-3 and LNCaP human prostate cancer cell lines generate prostate tumours when implanted subcutaneously or orthotopically in these mice [30]. While PC-3 (androgen-independent) tumours will metastasis to regional lymph nodes, bone metastases are rare. However, a subline of LNCaP cells, called C4, is capable of generating osteoblastic bone metastases and can grow in castrated mice, though derived from a line of androgen-sensitive cells [11]. Further culture of C4 cells taken from bone metastases, called C4-2 cells, were then introduced into tumour-naive nude mice. Interestingly, there was more rapid dissemination to bone with the C4-2 cells than the original cells [11]. This suggests that the target tissue (“soil”) may influence cancer cells, conferring on them a phenotype capable of more aggressive behaviour.

One criticism of the above models was that human prostate cancer cells may interact differently with human bone than murine bone. A further refinement was thus made on the model, in which human fetal bone was grafted intramuscularly in immunodeficient mice. PC-3 and LAPC-4 cells were then injected 2 mm away from the bone pieces. PC-3 bone metastases were found by immunohistochemistry to be osteoclastic (stained positively for PTHrP, tumour neurosis factor α (TNFα), and IL-6). By contrast, LAPC-4 cells, induced osteoblastic metastases, which stained positively for the above plus osteocalcin, a marker of bone formation [32]. As

animal models become more sophisticated, more focused and relevant experiments will continue to delineate molecular pathways and test targeted therapies.

4. Monitoring of bone metastases

Patients with bone metastases from prostate cancer are generally followed clinically with pain scores, biochemically with serum alkaline phosphatase, and radiologically with bone scans. Quantifying analgesic medication use and tracking pain scores can reliably estimate disease control in many patients [33]. These parameters may also correlate with quality of life, an important clinical outcome. Serum alkaline phosphatase, a marker of bone formation, is an early indicator of osteoblastic disease, and its level correlates with bony disease burden [34]. However, reduction in alkaline phosphatase is not always synchronous with clinical response to bisphosphonates, suggesting alternative tests for monitoring are still necessary [35]. Urinary pyridinium has been proposed as a more specific marker, reflecting response to therapy more accurately and correlating with disease burden [1]. However, it has not been correlated with outcomes, such as survival or skeletal events, and testing is not yet widely available.

Technetium 99m bone scans are generally used to screen for bony disease; they are sensitive, but not specific, and will reveal areas of tracer accumulation as a result of trauma, degenerative changes, infection and even disuse osteopenia in addition to tumour-related osteoblastic activity [36]. Stability or improvement in bone scans has been shown to correlate with survival [37]. However, after initiation of treatment, bone scans occasionally reflect a ''flare'' phenomenon in which metastases appear worse, though they are in fact responding. For this reason, there are recommendations to follow the number of lesions on bone scan rather than the intensity of lesions. In the future, fluorine-18 fluorodexyglucose-position emission tomographic (FDG-PET) scans may have a larger role in staging, as they can simultaneously identify metastases in soft tissues and bone. They are also capable of distinguishing cancer from non-malignant causes of abnormal tracer uptake on bone scans with high specificity (98%). However, they may not be able to replace bone scans, because of lower sensitivity for osseous metastases (approximately 65%), especially in bones such as the skull and ribs [38]. Computerised tomographic (CT) scans, while not traditionally used to follow bony disease, can detect metastases within the bone marrow before clinical destruction of bone is evident and can provide anatomical corroboration for areas of increased tracer uptake on bone scans [36]. Magnetic resonance imaging (MRI) can be extremely useful in evaluating the spine – it can detect lesions missed on bone scan; however interpretation must be approached cautiously, as high false-positive rates have been observed [39].

5. Management of painful bone metastases

Pain is frequently the most prominent clinical manifestation of metastatic prostate cancer, both directly from tumour destruction of bone, and from compromise of nearby nerves, inducing radiculopathy or plexopathy. Many of the cytokines that participate in the signalling between prostate cancer cells and osteoblasts, specifically IL-6 and TNF, can also directly stimulate nociceptors [40]. This makes anti-inflammatory treatment theoretically attractive. However, there are no long-term safety data for non-steroidal anti-inflammatory drugs (NSAIDs) in prostate cancer patients, and no specific data to confirm the widely taught precept that NSAIDs are more effective than opiates for bone pain. Rather, a combination is favoured, as multiple studies have found that adding an NSAID to an opiate regimen decreased opiate requirements and improved pain control without additional side-effects [41].

External beam radiation therapy is an effective treatment for individual symptomatic lesions; in Radiation Therapy Oncology Group (RTOG) 7402 complete pain relief was achieved in 54%, and partial pain relief in up to 90%, of patients with bone metastases from various primary cancer sites [42]. The shorter, larger-fraction course in this study was associated with more prompt pain relief in patients with multiple bone metastases. However, overall data are conflicting with regard to short courses being substituted for traditional protracted fractionation courses. A randomised, prospective study by the Royal Marsden Hospital found that a single dose of 8 Gy was equally effective compared with 30 Gy in 10 daily fractions in a mixed population [43]. By contrast, a retrospective look, divided into histological groups, found a positive correlation between total dose and efficacy. For prostate cancer specifically, 40 Gy resulted in superior outcomes compared with <40 Gy (75% complete pain relief versus 61%) [44]. Yet another strategy is encompassing multiple metastases in one extensive field, such as a hemi-body, with a dose of 25–30 Gy over 8–10 fractions. Toxicity limits its utility compared with multiple localised treatment plans or radioisotope therapy; with these larger fields, toxicity to lungs and intestines provokes severe complications in up to 30% of patients [45]. Further studies are warranted to determine the optimal radiation treatment field, dose and fractionation.

Bisphosphonates have been shown to be effective in controlling bone pain and hypercalcaemia, as well as in preventing fractures in metastatic prostate cancer [35,46,47]. Treatment with olpadronate was shown to reduce bone resorption, as measured by serum and

urinary calcium, as well as urine hydroxyproline [35]. Clinically, in the same group of patients, 76% experienced pain relief, with both decreased pain scores and discontinuation or reduction of opiate doses. In terms of prevention, a randomised controlled trial of patients with prostate cancer with metastasis to bone showed that zoledronic acid treatment resulted in an 11% absolute risk reduction for skeletal events, as well as a significant delay in the time to development of a skeletal event ($P = 0.009$) [47]. Skeletal events were defined as pathological fracture, spinal cord compression, additional surgery or radiotherapy to bone, or change in antineoplastic therapy in order to control bone pain. These benefits were achieved without significant toxicity. A cost-effectiveness analysis revealed that, while skeletal events were avoided and patients spent fewer days hospitalised, the expense per quality adjusted life-year saved was greater than generally held standards [48]. It is hoped that lengthier follow-up and decreased cost of bisphosphonates in the future will yield a more favourable cost–benefit ratio.

Bisphosphonates have high affinity for hydroxyapatite, and concentrate near osteoclasts, where bone mineral is exposed. They are thought to mediate their effect via direct actions on osteoclasts, such as interfering with adhesion, recruitment, cytoskeleton arrangement, differentiation, and survival [49] (Fig. 3). For clodronate, this may be accomplished by accumulation of toxic metabolites in osteoclasts. However, for the other bisphosphonates which are not metabolised, suppression of osteoclast activity may be mediated by inhibition of the mevalonate pathway. Additionally, in vitro data show that bisphosphonates interfere with the adhesion of PC3 prostate cancer cells to the bone matrix [50], which may prevent the development of new bone metastases.

There is some evidence to suggest a direct anti-neoplastic effect of bisphosphonates, perhaps via inhibition of growth factor release, alteration of the hydroxyapatite surface, or triggering apoptosis in tumour cells [51]. In a prospective, randomised trial of breast cancer patients with documented malignant cells in their bone marrow aspirates, clodronate reduced the development of bone and soft tissue metastases by 50% compared with placebo [52]. However, in a rat model of prostate cancer, treatment with a bisphosphonate delayed the time to development of cord compression from vertebral metastases, but did not affect the development of lung metastases, suggesting a bone-specific rather than general tumouricidal effect [53]. Whether or not bisphosphonates can prevent soft tissue or bone metastases, they will likely come into broader use in adjuvant therapy for the indication of ameliorating the bone density loss associated with long-term androgen deprivation.

Radioisotopes are an additional effective treatment, especially when bone metastases are too widespread to be effectively treated by localised external beam radiotherapy. Strontium-89, phosphorous-32, and samarium-153 (relative risk of approximately 80% in breast/prostate) are all equally effective for pain relief [54]. Rapid onset of pain relief, within 72 h in some patients, suggests that the mechanism of action is mediated by cytokines or osteoclasts rather than tumour shrinkage [56]. However, compared with localised radiotherapy, radioisotopes may be less cost-effective. The European Organisation for Research and Treatment of Cancer (EORTC) randomised 203 HRPC patients to strontium or local field radiotherapy, and found an overall survival benefit (11 months versus 7.2 months) of borderline statistical significance in favour of radiotherapy, which was also associated with lower overall cost [55]. There is an ongoing National Cancer Institute (NCI) Clinical Tnals Support Unit (CTSU) phase III trial of consolidation therapy with doxorubicin with or without strontium after induction chemotherapy for HRPC to explore the role of early radioisotope therapy.

Androgen deprivation is the optimal first-line treatment for painful bone metastases when they develop before androgen insensitivity, with relief noted as quickly

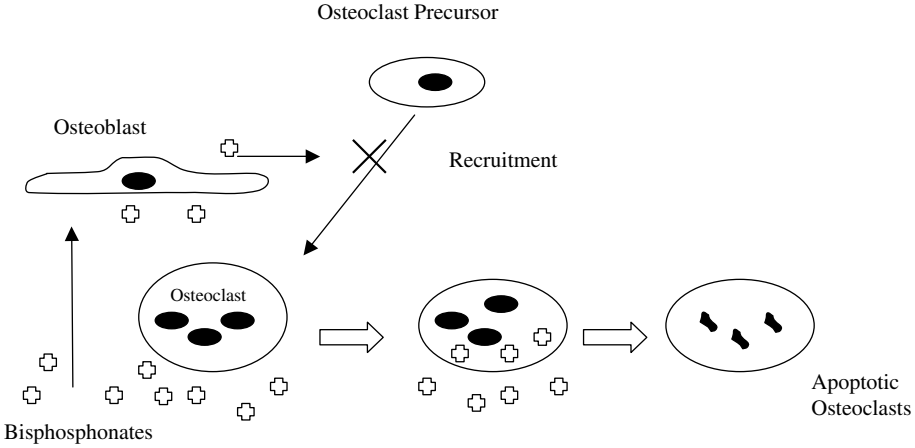

Fig. 3. Proposed mechanism of action of bisphosphonates for inhibiting bone resorption.

as 24 h after treatment [11]. This treatment controls bone disease for an average of 3–5 years [57]. Therapy should be initiated with a non-steroidal anti-androgen, such as flutamide or bicalutamide, prior to administering gonadotropin analogues in order to avert an increase in pain, or even fracture, from the flare phenomenon of GnRH-induced testosterone release. After the first dose, the gonadotropin analogue may be continued singly or in combination with the anti-androgen. Side-effects are generally mild, and include hot flashes, decreased libido, and erectile dysfunction. Intermittent androgen blockade has theoretical and early clinical promise; an ongoing South Western Oncology Group (SWOG) trial will determine whether it indeed delays the development of resistance to hormone manipulation therapy.

Traditional cytotoxic chemotherapy agents are also effective palliative agents for bone pain in metastatic prostate cancer patients. In fact, a study of 209 subjects randomised to mitoxantrone plus prednisone with or without clodronate revealed that palliation was equal on both arms, with 46% of patients achieving their palliative goals, and no additional benefit was derived from the addition of bisphosphonate therapy [58]. Palliation of bone pain is an important endpoint for clinical trials evaluating new cytotoxic therapies.

Recently the Food and Drug Administration (FDA) approved docetaxel (Taxotere) for first-line therapy in combination with prednisone. Its approval was based on the results of two multicentre, randomised phase III trials, presented at the American Society of Clinical Oncologists (ASCO) meeting in 2004. In SWOG 99-16, HRPC patients received docetaxel in combination with estramustine. Median survival was 18 months, compared with 15 months for the mitoxantrone arm [59]. In the international study presented by Eisenberger, 1006 patients were randomised to docetaxel every three weeks (arm A) or weekly (arm B) or to mitoxantrone (arm C). Median survival was 18.9 months for arm A ($P = 0.009$), 17.4 months for arm B ($P = 0.36$), and 16.5 months for arm C. Pain response was significantly better in both docetaxel arms, 35% and 31% compared with 22% for arm C ($P = 0.01$ and 0.08) [60].

6. Complications of bone metastases

In addition to causing pain, prostate cancer bone metastases may inflict morbidity by causing hypercalcaemia, pathological fractures, and spinal cord compression [3]. Hypercalcaemia is rare in prostate cancer, possibly because of limited bone resorption and because PTHrP, which would enhance distal collecting tubule reabsorption of calcium in addition to promoting osteoclast activity, is inactivated by PSA [24]. When hypercalcaemia does occur, treatment with intravenous fluid resuscitation and a bisphosphonate is indicated.

Pathological fractures cause substantial disability, particularly when they occur in the humerus or femur. The predominantly axial distribution of prostate cancer bone metastases [37] makes such events unusual; collapse of vertebral bodies is more frequent, and disability generally stems from nerve impingement. Bone scan activity in long bones should be promptly evaluated for prophylactic surgery and/or radiation, and extensive vertebral metastases should be considered for prophylactic radiation to avoid future cord compression [61].

Spinal cord compression may be the first presentation of prostate cancer in as many as 37% of cases and portends a poorer prognosis [11]. This is the most dreaded complication of bone metastases, as it causes pain and diminishes quality of life by compromising ambulation and bladder/bowel control. Specific treatment includes intravenous corticosteroid, preferably dexamethasone, to relieve odema and forestall spinal cord infarction. Neurosurgical decompression was shown in a randomised trial to yield superior functional outcomes over definitive radiotherapy, although survival was not affected [62]. Radiation therapy is an essential component of treatment after surgical decompression, and in cases where surgical intervention is not feasible or is contraindicated [63]. Pre-treatment function remains the best predictor of post-treatment function; it is critical to maintain a high index of suspicion to maximise early detection, and to treat vertebral metastases aggressively, focusing on prevention [64].

7. Molecularly targeted therapeutic approaches

Improved understanding of molecular pathways involved in the growth of bone metastases has led to identification of new targets for therapy (Fig. 4). As outlined earlier, RANKL is a final common pathway for signal amplification in osteoblasts, in response to growth factor and cytokine stimuli. Two compounds which compete with RANKL KB are in development, OPG and RANK-Fc [26,65]. RANKL primarily mediates bone resorption, and though this is the smaller arena of prostate cancer activity in bone, it may yield therapeutic benefit. Data from a mouse model are positive. However,

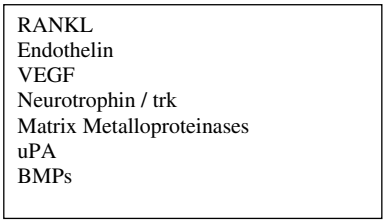

Fig. 4. Molecular targets of interest for therapeutic inhibition in prostate cancer metastatic to bone.

preliminary data from human studies are not yet available.

Endothelin stimulates growth of both osteoblasts and prostate cancer cells, making it a desirable target for pharmaceutical development. Atrasentan® (ABT-627), an oral ET_A receptor antagonist, has already shown clinical promise. In a randomised, placebo-controlled, phase II trial Atrasentan® delayed time to disease progression in HRPC patients. In the intention-to-treat analysis of 288 patients, the time to PSA progression was 155 days in patients taking 10 mg Atrasentan® compared with 71 days for those taking placebo ($P < 0.05$) [66]. Side-effects were mild to moderate, and included headache, rhinitis, and peripheral edema. Data from the randomised, placebo-controlled phase III trial were presented at ASCO 2004 by Carducci. Eight hundred and nine subjects participated, and there was a trend toward delayed time to progression in the Atrasentan® group, which was significant in a subset of protocol-compliant subjects. Smaller increases in PSA and alkaline phosphatase were noted in the Atrasentan® group ($P = 0.025$ and <0.001 respectively) [67]. Further studies are planned, such as combining Atrasentan® with docetaxel for first-line therapy in HRPC.

Vascular endothelial growth factor (VEGF) is a target of great interest in many cancers because angiogenesis is critical for tumours to maintain a supply of nutrients and oxygen. Experiments with fetal bovine osteoblast cell cultures have shown that VEGF is also capable of inducing differentiation of osteoblasts, although DNA synthesis was not stimulated [68]. Co-culture of a bone metastatic and HRPC cell line C4-2B with osteoblasts reveal that this metastatic prostate cancer cell line expressed 60% higher levels of VEGF than regular LNCaP cells [14]. Anti-VEGF agents may thus be useful in preventing bone metastases from HRPC; clinical data are awaited.

The neurotrophin/trk signal translocation axis has been shown to be involved in the regulation of and impaired survival pathology in prostate cancer cells. Malignant prostate epithelial cells strictly secrete a series of neurotrophins and express at least one of the trk receptor proteins (i.e. trk A, B, and/or C). Treatment with trk receptor tyrosine kinase inhibitors initiates apoptosis of malignant prostate cells, but not of normal epithelial cells [69]. Human osteoblasts were also shown to express trk receptors [69]. Proliferating osteoblasts have been documented to acquire a sensitivity to trk inhibitor-induced apoptosis not shown with normally quiescent osteoblasts [69], supporting the rationale for the use of trk inhibition to target the apoptotic death of both the prostate cancer cells and the proliferating osteoblasts in bone metastases. This is particularly appealing because such apoptosis should be possible without inducing the unwanted apoptosis of quiescent osteoblasts in areas of normal bone not involved in metastatic deposits. Phase II clinical trials with indocarbazole compounds, which are potent inhibitors of trk receptor signalling, are in process.

MMP inhibitors are under intense scrutiny, for reasons detailed in the pathophysiology section. In phase I trials, MMP inhibitors had a dose-limiting toxicity of myalgias and muscle inflammation [8]. Subsequent alterations in chemical structure have resulted in second-generation MMP inhibitors which have a broader range of substrates and lower rates of myalgias. Phase II and III data have been disappointing, despite attempts to combine them with traditional cytotoxic chemotherapy agents. In HRPC, for instance, the addition of prinomastat to mitoxantrone plus prednisone did not improve the time to disease progression [8]. Given that the promising preclinical studies were done in early stage disease [7], more benefit may be seen when these agents are tested in an adjuvant setting. Furthermore, it may be important to identify the specific pattern of MMP expression in prostate cancer, and choose a MMP inhibitor whose spectrum matches these targets. The ultimate success of this, and all targeted therapy, depends upon integration of all available molecular and pre-clinical data into appropriate clinical trial designs to facilitate the recognition of effective agents.

Conflict of interest statement

None declared.

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