Biology of bone metastases in prostate cancer

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ABSTRACT
Advanced-stage prostate cancer (PCa) patients are often diagnosed with bone metastases. Bone metastases remain incurable and therapies are palliative.

PCa cells prevalently cause osteoblastic lesions, characterized by an excess of bone formation. The prevailing concept indicates that PCa cancer cell secrete an excess of paracrine factors stimulating directly or indirectly osteoblasts, thereby leading to an excess of bone formation. The exact mechanisms by which bone formation stimulates PCa cell growth are mostly elusive.

In this review, the mechanisms of PCa cancer cell osteotropism, the cancer cell-induced response within the bone marrow/bone stroma and therapeutic stromal targets will be summarized.

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### 1. CLINICAL RELEVANCE OF BONE METASTASIS

Metastatic disease is the cause of 90% of human cancer deaths. Prostate cancer (PCa) is one of the most prevalent human cancers possessing a high propensity to metastasize to bone (osteotropism)[1]. Bone metastases are diagnosed in approximately 70% of advanced PCa patients. PCa, together with breast cancer, accounts for more than 80% of cases of bone metastatic disease. Cancer cell growth at the bone metastatic site causes a number of skeletal-related events, including severe pain, fractures, spinal cord/intervertebral nerve compression and hypercalcemia[2]. The ability of cancer cells to replace the hematopoietic bone marrow (myelophthisis), can also cause anemia and immunosuppression. Currently, bone metastases remain incurable and therapies are limited to the prevention of skeletal-related events and to control pain.

### 2. OSTEOTROPISM

Oscar Batson suggested that PCa cells disseminate to the vertebral column via the Batson plexus, a venous network that drains the prostate and, thereby, connects
the pelvic veins to the paravertebral venous plexus. However, the distribution of PCa skeletal metastases does not support the role of vertebral veins in the dissemination of this tumor. Currently, other mechanisms - also in combination - have gained more consensus:

**Hemodynamics of the bone marrow (BM).** The blood perfusion rate of the BM in the adult human is about 2.5 liter of blood flow each minute. Unlike in other organs, the arterial supply of the BM ends directly in large vessels (sinusoids). These are characterized by an endothelium allowing dynamic opening of pores within the endothelial cells themselves. The blood flow within the sinusoids is slow, in some areas almost stagnant. All these traits allow an easy egress of hematopoietic stem cells (HSCs) into the circulation, but also facilitate cancer cell extravasation and lodging in the BM. However, the observation that sinusoids are also part of the spleen, which is not prone to be a metastatic site, questions the exclusive role of the architecture of the BM sinusoids in the osteotropism of PCa.

**Adhesion molecules (“Homing receptors”, “Area code”).** Another possible mechanism explaining cancer cell osteotropism is the “key and lock” hypothesis. This hypothesis suggests that cancer cell-endothelium interactions mediate adhesion and extravasation specifically into the BM. These interactions are defined by cancer cell-expressed adhesion proteins engaging with cognate molecules specifically expressed on the luminal surface of the BM endothelium. A similar mechanism is adopted by leucocytes to arrest and extravasate at sites of inflammation, known as “area code”. Interestingly, endothelial cells of the BM vasculature express constitutively high levels of adhesive proteins, such as P- and E-selectins, intercellular adhesion molecule A and vascular adhesion molecule 1, which endothelial cells in other tissues only express after an inflammatory stimulus. Cancer cell expression of surface molecules, such as chemokine (C-X-C motif) receptor
(CXCR) 4/6/7 (CXCR4/6/7), integrins (in particular αvβ3 integrin), RANK, CD44, and annexin 2 receptor allow them to bind to endothelial cells and mediate homing to bone[3].

The most relevant homing mechanism explaining bone metastasis is the chemokine (C-X-C motif) ligand (CXCL) 12 (CXCL12)/CXCR4 axis. CXCL12, also known as stromal-derived factor 1, is a chemokine physiologically mediating HSC homing, survival and expansion in the BM. CXCL12 is the only known ligand for CXCR4. PCa cells express CXCR4 and, thus, are capable to detect chemokine gradients, which facilitates extravasation/migration of cancer cells to the BM stroma and binding to CXCL12-expressing BM cells, namely CXCL12-abundant reticular cells (pericytes and fibroblasts). CXCL12, the ligand-receptor binding, leads also to the up-regulation and activation of αvβ3 integrin in cancer cells which further facilitates cell adhesion to the BM extra-cellular matrix. In addition, signaling via CXCR4 promotes matrix metallopeptidase 9 and 13 expression in cancer cells, resulting in their increased migration and their survival/proliferation. Neutralizing antibodies to CXCR4 reduce the incidence of bone metastases in a PCa model [4].

The integrin αvβ3 integrin interacts with osteopontin, fibronectin and vitronectin. Expression of αvβ3 integrin on PCa cells correlates with a high incidence of bone metastasis. Targeting integrins can inhibit the de novo formation and progression of bone metastases in prostate cancer[5].

**The “Seed & Soil” hypothesis.** This hypothesis, originally postulated by Stephen Paget more than hundred years ago, has regained major consensus. It postulates that cancer cells, “the seed”, need a congenial microenvironment, “the soil”, in order to survive and grow. This implies that cancer cells disseminate randomly to all tissues, but succeed in growing only in those that are congenial. The BM/bone stroma is the congenial soil for PCa cells. BM can be either red or yellow, supportive
or hostile for hematopoiesis respectively. In particular, red BM provides a fertile soil for cancer cell growth. In the adult the red marrow is localized in the axial skeleton. Ultimately, cancer cells occupy completely the hematopoietic marrow, which eventually leads to a secondary activation of embryologically active BM. In that case bone metastases are observed in “exotic” places such as hands and feet.

3. “The “Seed And Soil” hypothesis in its modern interpretation”

3.1. Relationship between bone turnover and bone metastasis

In mouse models of systemic bone metastasis, cancer cells metastasize to the metaphysis of long bones. This is the site of most active bone formation and resorption (bone remodeling) in the mouse species. Parathyroid hormone administration prior to PCa cell inoculation stimulates bone turnover and increases skeletal colonization by cancer cells [6]. Conversely, decreased bone turnover lowers the incidence of bone metastases [7].

It has been reported that PCa patients can develop bone metastasis years or even decades after the primary tumor was excised. Interestingly, this time span is in line with the maximum time of complete skeletal remodeling of 10 to 20 years. It has been hypothesized that outgrowth of cancer cells to macrometastasis may be dependent on cancer cell location in close proximity to active bone remodeling sites (bone multicellular units) [7]. Furthermore, high bone turnover seems to predispose to relapse of cancer as bone metastasis. PCa patients are often treated with androgen deprivation therapy and the consequent increase of bone remodeling facilitates cancer cell growth at the bone metastatic site[8, 9].

Taken together, the evidence above suggests that factors released from the bone matrix during bone resorption or secreted during bone formation favor bone colonization, survival and expansion of cancer cells. Therefore, not the whole bone
tissue, but only discrete areas of bone modeling/remodeling, the bone multicellular units, represent a favorable “soil” for survival and growth of cancer.

3.2. Bone metastatic cancer cells compete with HSCs for their niche

Physiologically, stem cell behavior is controlled by intrinsic factors and extrinsic cues provided by an anatomically restricted, specialized tissue microenvironment, known as the stem cell niche. Stem cell niches support quiescence and maintenance of the stem cell pool, as well as stem cell expansion, differentiation and migration. Depending on their anatomical location in the BM, two major HSC niches have been described: an “endosteal/osteoblast” and a “vascular/perivascular niche”. The vascular niche consists of various cell types, namely endothelial cells, mesenchymal stem cells, CXCL12-expressing mesenchymal progenitors comprehending CXCL12-abundant reticular cells, leptin receptor-positive stromal cells and nestin-positive pericytes[10]. However, the current view suggests that the endosteal and vascular niche should be regarded not as two different compartments, but rather as a single entity. This is also consistent with the tight spatial and temporal coupling existing between osteogenesis and angiogenesis[11].

PCa cells that successfully metastasize and initiate growth have stem-cell like characteristics. The existence of a bone metastatic niche has been long debated, until shown that PCa cells occupy the same BM niche as HSCs [12]. These studies also showed that PCa cells promote the differentiation and decrease the number of HSCs. However, cancer cells not only occupy pre-existing stem cell niches, but also create their own niche. At the bone metastatic site PCa cells amplify the existing hematopoietic niche and induce de novo an ectopic epithelial tissue-of-origin niche (developmental prostate niche) [13]. The tissue-of-origin niche together with the amplified hematopoietic niche generates a hybrid niche, which is only supportive for
cancer cell growth, which explains the hematopoietic aplasia (myelophthisis) occurring in bone metastasis.

3.3. Survival, exit of dormancy of cancer cells at the bone metastatic site

Cancer cells may survive as non-proliferating (dormant) and never exit that stage to create a secondary tumor. At this point cancer lesions are microscopic and classified as micrometastases. In response to bone-specific factors, SRC kinase is activated which mediates AKT signaling, supporting survival of disseminated tumor cells. Only few cancer cells might evade growth-suppressive signals from the stroma or receive appropriate signals from the surrounding stroma and start proliferating to progress from micrometastasis to clinical relevant macrometastasis. As explained above, these “successful” cancer cells may have stem cell-like characteristics and be in close proximity to active bone multicellular units. Such stem-cell like PCa cells survive most therapeutic approaches such as androgen deprivation therapy[14] and thus may be responsible for progressive disease after treatment.

The complex changes necessary for dormant cancer cells to exit the quiescence stage and develop into overt bone metastasis are still largely unknown. A recent study showed at the metastatic site that fibrosis created by collagen 1 enrichment is a critical determinant of cytoskeletal reorganization in dormant tumor cells, which leads to an exit of dormancy and initiates metastatic growth [15]. Additionally, urokinase-type plasminogen activator receptor might be an essential molecule in dormant BM cancer cells, and involved in reactivation of their proliferation. It has been also shown that dormancy is lost in regions of sprouting vasculature due to a loss of thrombospondin 1 and the activation of transforming growth factor beta and periostin[16].
3.4. Phenotypes of bone metastasis

Once disseminated tumor cells start proliferating at the bone metastatic site, normal bone physiology is severely perturbed. Cancer cells either stimulate bone formation (osteoblastic bone metastasis) or stimulate bone resorption and block bone formation (osteolytic bone metastasis). On radiography osteoblastic lesions appear as radio-dense and osteolytic lesions as radio-transparent (Figure 1). PCa preferentially induces an osteoblastic response. In many patients osteoblastic and osteolytic bone metastatic lesions co-exist which might be due to the fact that heterogeneous cancer cells shed from the primary tumor and independently succeed to develop into overt metastasis. However, this view is challenged by copy number analysis of cancer cells within and between heterogeneous bone metastatic lesions which pointed to the origin from a single precursor cancer cell[17].

Both osteolytic and osteoblastic bone metastasis are prone to fracture either because of increased bone resorption or because newly deposited bone is mostly immature, “woven bone”, which is less mechanical competent than mature, lamellar bone.

3.5. Factors modulating osteoblast recruitment and activity

A number of osteoinductive cancer cell-derived factors stimulate mesenchymal progenitor cell recruitment and commitment to the osteoblast lineage rather than stimulating osteoblast activity.

Cancer cell-derived Wnts (Wnt 3a/7b/10b), bone morphogenetic protein (BMP) family members (BMP4/6/7), transforming growth factors, fibroblast growth factors and platelet-derived growth factors induce osteoblastic activity. Blocking Wnt activity convert the osteoblast response induced by the PCa cell line C4-2B tumors in osteolytic [18]. PCa cells produce BMP6, which concur to the osteoblastic response, and increased BMP6 expression in primary PCa correlates with the aggressiveness
of tumors [19]. It has been shown that PCa cells that have metastasized to bone have an up-regulated insulin-like growth factor 1 regulatory system, which promotes osteoblastic metastasis [20]. PCa cell-derived prostate-specific antigen activates parathyroid hormone-like hormone (PTHLH) and may cleave/activate also other growth factors such as insulin-like growth factor 1 and transforming growth factor beta, which further supports cancer cell growth and osteoblast-mediated bone formation [21].

Osteoblastic cancer cells are also characterized by the absence of bone resorbing cytokines and Wnt/BMP antagonists [22]. Overexpression of noggin in the PCa cell C4-2B abolishes the osteoblast response, thus emphasizing the role of BMPs and their antagonists in osteoblastic bone metastasis [22].

Cancer cell-derived endothelin 1 binds to endothelin A receptor (ET-AR) on osteoblasts, increasing osteoblast proliferation and new bone formation by activation of Wnt signaling pathway through suppression of dickkopf 1 [23, 24]. PCa patients with osteoblastic bone metastasis show high serum levels of endothelin 1. ET-AR inhibitors reduce the formation of bone metastasis and tumor burden [25].

Various PCa cell lines express vascular endothelial growth factors, which are capable to stimulate directly osteoblast recruitment. Inhibiting the receptors of vascular endothelial growth factors decreases intra-tibial tumor burden and PCa cell-induced osteoblastic activity showing that vascular endothelial growth factors contributes to PCa-induced osteoblastic response [26].

3.6. Factors modulating osteoclast recruitment and activity

**Cancer cell-derived osteoclastogenic factors.** Cancer cells can disrupt the balance of Nuclear factor kappa B (NF-κB) ligand (RANKL)/RANK (RANKL receptor)/osteoprotegerin not only by PTHLH.
Cancer cell-derived interleukin (IL) 8 (IL8) can directly stimulate osteoclastogenesis in a RANKL-independent manner. IL8 binds to its receptor CXCR1 on osteoclast precursors and osteoclasts and, thereby, stimulates osteoclastogenesis [27]. Many osteolytic cancer cell lines have been reported to express the osteolytic cytokines RANKL, colony stimulating factor 1, IL6 and tumor necrosis factor α. IL6 and tumor necrosis factor α indirectly stimulate osteoclastogenesis through the production of RANKL by osteoblasts.

Breast cancer cells express cyclooxygenase 2, which generates prostaglandin E2. Prostaglandin E2 increases RANKL in both osteoblasts and stromal cells. Cyclooxygenase 2 is also known to induce the expression of the osteolytic cytokines IL8 and IL11 [28].

In PCa bone metastasis, osteoclast-derived matrix metallopeptidase 7 cleaves RANKL to a soluble form that stimulates osteoclastogenesis [29]. Matrix metallopeptidase 13 and cathepsin G, overexpressed at the tumor/bone interface, as compared to normal bone, activate matrix metallopeptidase 9, which, in turn, releases active RANKL and transforming growth factor beta from their latent forms [30, 31].

**Cancer cell-derived factors inhibiting bone formation.** Osteolytic metastases are also a result of reduced bone formation. Multiple myeloma cells overexpress dickkopf 1, a Wnt antagonist, thus, interfering with mesenchymal stem cell/osteoblast progenitor differentiation into OBs. Likewise, PCa cells secrete the BMP antagonist noggin, which impairs bone formation, thereby, worsening the osteolytic lesion [32].

### 3.7. Factors promoting cancer cell growth at the bone metastatic site

*The “Vicious cycle” hypothesis of bone resorption and tumor growth in osteolytic bone metastasis.* This hypothesis assumes that osteolytic cancer cells
secrete numerous growth factors, the most relevant being PTHLH, which, in turn, stimulates osteoblasts to secrete RANKL. RANKL binds RANK on osteoclast progenitor cells, which then stimulates osteoclastogenesis and, consequently bone resorption. This process releases various growth factors embedded in the bone matrix, including transforming growth factor beta, insulin-like growth factor 1 and calcium ions, which further fuel cancer cell growth and secretion of PTHLH, thus amplifying and perpetuating the process (Figure 2). Transforming growth factor beta is considered as the major factor that, once released from the bone matrix, supports cancer cell expansion. In mouse models of systemic bone metastasis, interference with the transforming growth factor beta pathway in cancer cells caused fewer and slower progressing metastasis [33]. PCa cells express calcium-sensing receptor and can therefore respond to ionized calcium released during bone resorption with increased proliferation and stimulation of PTHLH release [34].

The “Vicious Cycle” hypothesis provided the basis for the inhibition of bone resorption as a strategy to interfere with bone metastatic tumor growth. However, the “vicious cycle” remains a hypothesis to be still demonstrated, since in animal models of bone metastasis bisphosphonates (BPs) treatment effectively abolishes bone resorption, however, cancer cell proliferation persists, with no effect on total tumor burden [7]. Furthermore, in the clinical setting BPs inhibition of bone resorption is an effective strategy to reduce skeletal-related events, a direct negative impact of BPs on cancer cell growth and tumor mass remain only anecdotal. This observation suggests that other mechanisms than bone resorption support cancer cell growth at the bone metastatic site.

**Pro-angiogenic factors.** One of the early events, both in primary tumors and in bone metastasis, is the stimulation of angiogenesis by cancer cell-derived factors. However, the role of angiogenesis in bone metastasis is almost unexplored. Only
few studies have investigated the role of angiogenesis in osteolytic bone metastasis [35] or shown an inhibitory effect of anti-angiogenic therapy on both osteoblastic response and tumor burden in mouse models of osteoblastic bone metastasis [26, 36].

Extra-cellular matrix-remodeling factors. Cancer cell- and stromal-derived proteolytic enzymes are involved in various processes, such as matrix degradation, cell migration/invasion and angiogenesis. Matrix metallopeptidase and cathepsin K mediate extra-cellular matrix remodeling, cleavage of latent growth factors and release of matrix-bound growth factors, which then lead to the induction of angiogenesis increasing the recruitment of vascular progenitor cells. In human tumor specimens it has been shown that different members of the urokinase-type plasminogen activator system are increased at the metastatic sites compared to primary tumors. The plasminogen system is involved in processes such as cell adhesion, differentiation, proliferation and migration, e.g. via plasmin degradation of fibrin or vitronectin.

Hormones. Bone remodeling increases following menopause and surgical or chemical castration. PCa patients are often treated with androgen deprivation therapy and the consequent increase of bone remodeling facilitates cancer cell growth at the bone metastatic site.

Physical properties. Various physical properties, such as hypoxia and low pH, support cancer cell growth at the bone metastatic site. Hypoxia increases osteolytic bone metastasis by inhibiting osteoblast differentiation and increasing osteoclastogenesis. Low pH stimulates directly osteoclasts and the activity of proteolytic enzymes and, therefore, shifting the acid-base balance in the alkaline direction might be beneficial for bone loss disorders [37].
“Vicious cycle” in osteoblastic bone metastasis? The identity of the osteoblast-derived survival/growth support for osteoinductive cancer cells is almost unexplored. Recently it has been shown, that osteoinductive PCa cells induce osteogenesis and angiogenesis in the BM/bone stroma, which translates in an amplification of hematopoietic and prostate epithelial stem cell niche components [13] (Figure 3).

Stroma-derived cytokines (transforming growth factor beta and BMPs), chemokines (CXCL12) and extra-cellular matrix components (collagen type I peptides) have been shown to stimulate in vitro migration and proliferation of osteoinductive PCa cell lines [38]. Likewise, co-cultures of human bone stromal cells and human PCa cells have been shown to induce stromal cell expression of extra-cellular matrix (versican, tenascin) and chemokines (brain-derived neurotrophic factor, chemokine (C-C motif) ligand 5, CXCL5, and CXCL16), which increases cancer cell growth [39].

4. THE STROMA OF BONE METASTASIS AS A THERAPEUTIC TARGET

As already pointed out, all treatment options available for bone metastasis are palliative. Patients with bone metastasis in selected cases may undergo surgery or receive radiotherapy/chemotherapy in order to control cancer cell proliferation and pain. Various other treatment options exist to manage bone pain (opioids), prevent skeletal-related events (BPs) and bone fractures (injection of bone cement).

4.1. Pharmacological interference with the bone stroma support in osteolytic bone metastasis: inhibitors of bone resorption

The main strategy aims to inhibit bone resorption and, therefore, to disrupt the “vicious cycle”. However, there are also various alternatives, either already in clinical use or currently evaluated in clinical trials.
**Bisphosphonates (BPs).** BPs are hydrolysis-resistant inorganic pyrophosphate analogues, in which a carbon atom exchanged the bridging oxygen atom (P-C-P backbone). The two oxygen atoms of the phosphonate groups chelate divalent metal ions and, therefore, BPs bind avidly the hydroxyapatite crystals composing the bone mineral. Most BPs used in clinical setting contain an additional hydroxyl group attached to one of the side chains, which further increases the affinity. The second side chain classifies BPs into simple BPs or nitrogen-containing BPs (N-BPs). Most BPs are administered intravenously due to their poor oral bioavailability. Approximately 50% of circulating BPs are integrated into the bone mineral, where it has a half-life ranging from 1 to 10 years in humans. The remaining, circulating BP is rapidly eliminated via the kidney.

The most prominent effect *in vitro* and *in vivo* is the inhibition of osteoclastic bone resorption and the induction of their apoptosis. Depending on the class of BPs, osteoclast inhibition is mediated via one of the following mechanisms: a) simple BPs are intra-cellularly metabolized to toxic analogues of adenosine triphosphate, whereas b) N-BPs inhibit mainly farnesyl pyrophosphate synthase. Inhibition of this synthase causes a depletion of prenylated proteins, such as small guanosine triphosphate enzymes, which are signaling proteins regulating important cell processes important for osteoclast function and survival (e.g. integrin signaling and membrane ruffling). In addition, they induce apoptosis by accumulation of metabolites of the mevalonate pathway, which are converted to toxic adenosine triphosphate analogues.

Besides a direct effect on osteoclasts, BPs may affect other cell types. *In vivo*, they inhibit angiogenesis and decrease the number of tumor-associated macrophages as shown in a breast cancer mouse model. *In vitro*, BPs induce tumor-
associated macrophages to reverse-polarize from pro-tumoral M2 to anti-tumoral M1 phenotype.

Direct effects on cancer cells still remain controversial. *In vitro*, N-BPs inhibit PCa cell proliferation at high concentration (>10μM), whereas adhesion and invasion [40] of breast cancer and PCa cells is inhibited at lower concentrations (10E-12 to 10E-06 M).

*In vivo*, BPs inhibit bone metastasis and reduce tumor burden ([41-43]. However, studies showed that BP treatment had no effect on tumor burden in already established bone metastasis (*curative setting*) [7, 44]. BP administration prior to intra-cardiac injection of cancer cells reduced the number of developing bone metastases [7].

Clinical trials have shown that BPs treatment are effective in reducing skeletal-related events and bone pain in bone metastatic breast cancer and PCa, but exerts only a limited or no impact on survival[45].

**Neutralizing RANKL antibody and inhibition of activin receptor.** The use of a RANKL neutralizing antibody increased the onset of first skeletal-related events in patients with advanced solid cancer when compared to BPs [46]. Due to its higher activity and easier galenic form for application it has replaced the use of BPs in daily clinic.

Activin is a member of the transforming growth factor beta superfamily known to increase bone mass *in vivo*. In a mouse model of human breast cancer, inhibition of activin A was effective to prevent bone metastasis [47].

**Inhibition of cathepsin K and SRC-kinase.** Cathepsin K is an essential protease secreted by osteoclasts during bone resorption, as demonstrated in cathepsin K knock-out mice. The efficacy of a cathepsin K inhibitor in reducing osteolysis and skeletal tumor burden has been validated in two mouse breast cancer models. In the
a cathepsin K inhibitor is in phase III development for the treatment of osteoporosis. At 5 years, women treated compared to placebo showed a higher bone mineral density [48].

SRC is a non-receptor tyrosine kinase expressed abundantly in many different cell types. SRC regulates osteoclast function and migration, but it is also a negative regulator of osteoblasts. SRC-kinase knock-out mice display an osteopetrotic phenotype, suggesting that therapeutic SRC-kinase targeting may not show collateral effects. Dasatinib, a small molecule tyrosine kinase inhibitor, blocks the SRC family of tyrosine kinases and certain receptor tyrosine kinases (e.g. colony stimulating factor 1 receptor/c-fms). A phase II trial in PCa patients with bone metastasis, treated patients showed slower disease progression and reduced bone turnover and tumor burden [49].

4.2. Pharmacological interference with the bone stroma support in osteoblastic bone metastasis

Osteoblastic bone metastasis are composed of immature woven bone that is less mechanically competent and, thus, prone to fracture. Therefore, anti-resorptive agents are administered also in this case with the aim to prevent skeletal-related events.

Inhibition of ET-AR. In a breast cancer mouse model, inhibition of ET-AR was shown to reduce number of bone metastases and tumor burden. However, the clinical efficacy of the ET-AR inhibitor atrasentan is controversial. A phase II clinical trial in PCa patients with bone metastasis has shown a delay in disease progression that, however, could not be confirmed in a subsequent phase III trial[50].
**Inhibition of angiogenesis.** Tasquinimod, a quinoline-3-carbox-amide derivative, up-regulates thrombospondin 1 and down-regulates vascular endothelial growth factor, CXCR4, lysyl oxidase, CXCL12 and S100A9, which are important molecules implicated in tumorigenesis and angiogenesis. In patients receiving tasquinimod bone alkaline phosphatase levels were stabilized.

**CONCLUSIONS**

The prevention and treatment of PCa bone metastases remains one of the biggest clinical challenges in the management of this disease. Once patients develop bone metastasis, treatment options are palliative. Better understanding and knowledge of the mechanisms behind this propensity to form bone metastases will lead to new treatment approaches.

**ABBREVIATIONS**

BMP = bone morphogenetic protein; BM = bone marrow; BP = bisphosphonate; CXCL = chemokine (C-X-C motif) ligand; CXCR = chemokine (C-X-C motif) receptor; ET-AR = endothelin A receptor; HSC = hematopoietic stem cell; IL = interleukin; PCa = prostate cancer; PTHLH = parathyroid hormone-like hormone; RANKL = nuclear factor kappa B (NF-κB) ligand
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FIGURE LEGENDS

Figure 1. Bone metastasis visualized using a bone scan and radiography. A. Bone scan after injection of a radioactive tracer showing multiple metastases (dark spots). B. Osteoblastic bone metastasis in the spine and pelvic area evident as radio-dense areas on radiographs. C. Osteolytic bone metastasis in the pelvic area evident as radio-transparent areas on radiographs. Sources: A and B GN. Thalmann, Department of Urology and Department of Clinical Research, University of Bern, Switzerland. C. http://www.hopkinsarthritis.org/physician-corner/rheumatology-rounds/round-2-treatment-of-metastatic-bone-disease/.

Figure 2. The vicious cycle hypothesis of bone resorption and tumor growth. Osteolytic cancer cells secrete numerous growth factors (e.g. PTHLH), which stimulates osteoblasts to secrete RANKL. RANKL binds to its receptor (RANK) on osteoclast progenitor cells, which in turn stimulates osteoclastogenesis and consequently bone resorption. This process releases various matrix-embedded growth factors, such as calcium and phosphate, which further fuel cancer cell growth and secretion of PTHLH, thus amplifying and perpetuating the process.

Abbreviations: osteoprotegerin (OPG), receptor activator of NF-kappa-B ligand (RANKL), receptor of RANKL (RANK).

Figure 3. Mechanistic scheme of osteoblastic bone metastasis. Osteoinductive cancer cells secrete a number of factors stimulating progenitor cell recruitment and commitment of these progenitors to the osteoblast lineage. The identity of released factors by osteoblasts fueling cancer cell growth is mostly elusive. However, it has been recently shown that osteoinductive cancer cells induce osteo- and angiogenesis in the BM/bone stroma, thereby expanding the pre-existing hematopoietic niche.

Abbreviation: mesenchymal stem cell (MSC).