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Differences of osteoblastic bone metastases and osteolytic bone metastases in clinical features and molecular characteristics

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Abstract Several cancers tend to metastasize to bone, leading to osteolytic or osteoblastic bone lesions. The respective phenotypes of bone destruction and bone formation vary in clinical features, including incidence, prognosis, skeletal-related events and bone biomarkers. In addition, different molecular mechanisms explain the difference in phenotype. For example, molecules involved in osteolytic bone metastases (represented with breast cancer) include parathyroid hormone-related protein, transforming growth factor-β, while in osteoblastic lesions (represented with prostate cancer), endothelin-1 and morphogenetic proteins, etc. play a more important role in bone formation. It is important for us to understand the differences of bone metastases between two phenotypes to help clinicians to understand the underlying mechanisms, behaviors and therapies in development and currently available for bone metastases.

Keywords Bone metastases · Differences · Clinical features · Molecular characteristics · Bone targets

Introduction

Certain solid tumors, such as breast, prostate cancer and lung cancer, tend to metastasize to bone [1, 2]. When skeleton metastases happen, usually, there are two types of lesions: osteoblastic or osteolytic, which result from an imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption [3]. Osteoblastic bone metastases are usually seen in prostate cancer. In contrast, many solid tumors, including cancers of breast, lung, thyroid and renal, tend to form osteolytic metastases which are much common than osteoblastic lesions. It must be noted that both bone resorption and formation can be observed in most cancer types, with patients exhibiting both components to different degrees [1]. This difference in bone lesions indicates the different underlying mechanisms in forming osteoblastic or osteolytic lesions, leading to different treatment targets. In addition, there are many differences in clinical features between two bone metastases. In this review, differences in clinical features and molecular characteristics between osteoblastic bone metastases and osteolytic bone metastases will be discussed to help clinicians to understand the underlying mechanisms, behaviors and therapies in development and currently available for bone metastases.

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Differences of bone metastases in clinical features

Incidence of bone metastases

The incidences of dysregulated osteolysis and abnormal bone formation both vary according to the primary tumor. A postmortem examination in different cancers showed that up to 70 percent of patients with advanced breast or prostate cancer suffered from this complication [4]. Other cancers including thyroid, kidney and lung also bear an incidence of 30–40 % to form bone metastases. Gastrointestinal cancer rarely produces bone metastases with an incidence only <10 % [4] (Table 1).

Table 1 Differences of osteoblastic bone metastases and osteolytic bone metastases in clinical features

Clinical features	Osteoblastic bone metastases	Osteolytic bone metastases	
	Prostate cancer	Breast cancer	Lung cancer
Incidence	68 %	73 %	36 %
Median survival time	24 months	32 months	7 months
Total SREs	49 %	68 %	48 %
Radiation to bone	33 %	43 %	34 %
Pathologic fractures	25 %	52 %	22 %
HCM	1 %	13 %	4 %
Surgery to bone	4 %	11 %	5 %
Spinal cord compression	8 %	3 %	4 %
Bone biomarkers	Bone formation markers	Bone resorption markers and osteoclast regulators	
	BALP, OC, P1CP, P1NP, etc.	PYD, DPD, CTX, NTX, BSP, ICTP, RANKL, OPG, etc.	

Data adapted from ref. [4, 8–12] presented as a table

BALP Bone alkaline phosphatase, *OC* osteocalcin, *P1CP* C-terminal propeptide of procollagen type 1, *P1NP* N-terminal propeptide of procollagen type 1, *PYD* pyridinoline, *DPD* deoxypyridinoline, *CTX* C-telopeptide of type I collagen, *NTX* *N*-telopeptide of type I collagen, *ICTP* pyridinoline cross-linked carboxyterminal telopeptide of type I collagen, *BSP* bone sialoprotein, *RANKL* Receptor activator of nuclear factor-κB ligand, *OPG* Osteoprotegerin

Prognosis

Notably, once tumor metastasizes to bone, it is incurable. The survival time after diagnosis varies among different tumor types. A study that analyzed the prognostic factors for survival in patients with spinal metastases demonstrated that the average survival time for patients with prostate, thyroid, breast and rectal cancer was longer than that of stomach and lung cancer, and it also suggested that type of primary tumor was the most powerful prognostic factor [5]. The 5-year survival rate is only 33 % for patients with distant prostate cancer metastases and 26 % for those with breast cancer [6]. Median survival of breast cancer or prostate cancer after the diagnosis of bone metastases is approximately 2–3 years [7]. However, the median survival of lung cancer with bone metastases is 6–7 months [8]. Recently, a retrospective observational study showed that the median overall survival after diagnosis of prostate cancer with spinal metastases was 24 months with an estimated 1-year overall survival of 73 % [9]. The median survival time after diagnosis of breast cancer with bone metastases was 32 months [10].

SREs

Both osteolystic and osteoblastic bone lesions tend to metastasize to the axial skeleton, such as rib sternum, pelvis and vertebrae, leading to skeletal-related events (SREs), which mean pathologic fractures, spinal cord compression, severe pain requiring radiotherapy or surgery and hypercalcemia [1]. Among all tumor types, patients with breast cancer have the highest incidence of skeletal complications, approximately 70 % [11]. The incidence of SREs of prostate cancer is 50 %, close to lung cancer and other cancers. The most common SREs in all tumor types are radiation to bone and pathologic fracture.

Bone biomarkers

Many bone metabolism markers elevated in bone metastases are closely associated with disease progression and treatment efficacy [12]. Some of them may have potential prognostic value and help clinicians diagnose bone metastases, determine treatment and monitor efficacy. For example, the bone resorption markers *N*-telopeptide of type I collagen (NTX) and bone alkaline phosphatase (BALP) are associated with higher rates of death and SREs in prostate cancer bone metastases and also provide prognostic information in patients receiving zoledronic acid and denosumab [13, 14]. Similar results are also found in lung cancer and other solid cancers [15]. Although bone markers are divided into bone formation markers and bone resorption markers, it must be noted that both of them increase in most bone metastases cases (Table 1). Usually, bone resorption happens before bone formation. Therefore, bone resorption markers could be an earlier detection tool in bone metabolism than bone formation markers.

Differences of bone metastases in molecular mechanisms and therapeutic implications

Bone metastasis is a multi-step process, involving the interplay between tumor cells and the bone microenvironment where various signaling pathways and molecules

participate in to form a vicious circle and promote tumor cell and bone metastases [16]. Tumor-induced osteoblastic and osteolytic activities are different and play different roles in supporting their growth and survival, leading to different therapeutic implications [16]. It is important to better understand molecular mechanisms to break the vicious cycle.

Molecular mechanisms and therapeutic implications in osteoblastic bone metastases in prostate cancer

Osteoblastic bone metastases in prostate cancer are caused by tumor-derived factors that lead to osteoblast proliferation, differentiation and bone formation. Compared to models of osteolytic metastases, osteoblastic models are rare. The mechanisms that determine a metastatic lesion being osteoblastic or osteolytic remain unclear.

Endothelin-1 (ET-1) has been suggested to be a central mediator of osteoblastic metastases which stimulates the new bone formation via the endothelin A receptor (ETAR) in mice and humans [17]. ET-1 has been found increased in patients with bone osteoblastic lesions, especially in androgen-independent advanced prostate cancers [18]. Downstream genes of ET-1 with possible roles in osteoblast function include IL-6, Wnt5a, connective tissue growth factor (CTGF) and receptor activator of nuclear factor kappa-B ligand (RANKL) [19]. Importantly, ET-1 significantly suppresses the DKK-1 which is a negative regulator of the Wnt signaling pathway [20]. ET-1 can also enhance the mitogenic effect of other growth factors such as insulin-like growth factor 1 (IGF-I), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) [21]. In a mouse model, the ETAR antagonist atrasentan prevents osteoblastic bone metastases and reduces skeletal morbidity [22, 23]. Clinical trials indicate atrasentan seems to prolong time to disease progression (TTP), prostate-specific antigen (PSA) and BALP increase, although TTP does not reach statistical significance compared to control group [24]. However, a recent clinical trial indicated that ZD4054, another ETAR antagonist, did not prolong OS or TTP in patients with castrate-resistant prostate cancer (CRPC) with bone metastases [25, 26]. The negative results were also found in a phase III clinical trial with combined ZD4054 and docetaxel [27]. Unexpectedly, these therapies are not proven efficacious in limiting disease progression. However, it is possible that these drugs could be used to combat the development of osteoblastic lesions where there is a clear osteoblastic event which may impact life quality, becoming progressively worse if not treated. Furthermore, identification of patient subgroups based on either clinical characteristics or biomarkers may help better define people most likely to benefit from ETAR-targeted therapy in future clinical trials.

As mentioned above, *DKK-1* is a negative regulator of Wnt proteins which are tumorigenic and osteogenic potential [28]. Elevated levels of Wnt proteins play an important role in the development of osteoblastic metastases [29]. DKK-1 inhibits Wnt canonical signaling by binding to the lipoprotein receptor-related protein (LRP) receptor, leading to internalization of the receptor. Moreover, it has been reported that DKK-1 inhibits the secretion of osteoprotegerin (OPG) and induces RANKL, which are important for osteoclastogenesis [30]. One study showed that blocking DKK-1 expression in osteolytic PC-3 prostate cancer cells induced osteoblastic activity and, conversely, inducing DKK-1 in the mixed osteoblastic/osteolytic prostate cancer C4-2B cell line resulted in experimental osteolytic bone metastases [31]. DKK-1 might determine prostate cancer bone metastases transit from osteolytic to osteoblastic [32]. However, a recent study demonstrated that DKK-1 significantly promoted prostate cancer growth and increased the incidence of bone metastases which has also been confirmed in myeloma and breast cancer [33, 34]. The probable mechanism is DKK-1 increases phospho46 JNK by the Wnt noncanonical pathway. Different types of cancer and different stages of cancer may be intrinsically caused by differing effects of the Wnt pathway [32]. Another explanation is that DKK1 might bind other proteins and have distinct, unknown mechanisms of action. The role of DKK-1 in bone metastases is not fully understood.

Bone metastases of prostate cancer tend to be osteoblastic, while the osteolytic factor parathyroid hormone-related protein (*PTHrP*) is also highly expressed in prostate cancer. A proposed explanation is that PTHrP can also stimulate bone formation by activating the ETAR with NH2-terminal fragments of PTHrP which share strong sequence homology with ET-1 [35]. It has also been shown that there are strong anabolic responses to PTHrP fragments 1–20 and 1–23. The PSA, an important indicator in prostate cancer diagnosis and treatment, may inactivate the osteolytic effects of PTHrP [36].

Bone morphogenetic proteins (*BMPs*) are well recognized to promote bone growth by directly simulating differentiation of osteoblast precursors to mature mineral-producing osteoblasts [37, 38]. Several researches indicate an autocrine effect of BMPs on prostate cancer cells, promoting cell invasion and migration [39, 40]. BMP4 is found to promote osteogenesis in the progression of prostate cancer in bone by modulating BMP4-mediated paracrine signaling [41]. Prostate cancer also promotes osteoblastic activity through BMP-6 and BMP-6 antagonist, noggin, could be a novel strategy treatment of osteosclerotic bone metastases of prostate cancer [42]. Noteably, a recent study suggested that the combined application of RANK-Fc, a recombinant RANKL antagonist and RN, a

retroviral vector expressing noggin effectively inhibited the progression of mixed osteolytic/osteoblastic prostate cancer lesions in bone [43]. RANK-Fc alone inhibited osteolysis, while RN alone inhibited the osteoblastic component in a mixed lytic/blastic lesion. As the role of RANKL in osteolytic bone lesions is widely studied, this study confirms the role of BMP mainly in promoting osteoblastic lesions. This study also indicates the different applications of bone-targeted drugs based on the type of bone metastases.

Other factors such as PDGF, IGF, urokinase-type plasminogen activator (uPA) are also implicated in increasing osteoblastic bone metastases [36, 44].

Molecular mechanisms in osteolytic bone metastases in breast cancer

Breast cancer cells secrete many osteotropic cytokines to stimulate osteolysis, such as PTHrP, tumor necrosis factor α (TNF-α), interleukins, leukemia inhibitory factor (LIF) and receptor activator for RANKL [45, 46].

PTHrP is an important osteoclast-activating factor which is elevated in 90 % of bone metastases samples [47]. PTHrP activates osteoclasts and promotes bone resorption by binding to its receptor present on osteoblasts [48]. PTHrP upregulates RANKL and downregulates OPG by interacting with parathyroid hormone receptor 1. Also, PTHrP can promote tumor cells proliferation by autocrine action and tumor angiogenesis [49, 50]. Linforth et al. demonstrated that co-expression of PTHrP in early breast cancer indicated poor prognosis, while a recent study found that PTHrP expression in primary tumor was associated with improved survival and fewer bone metastases [51, 52]. Antibodies against PTHrP are reported to suppress osteolytic bone metastases and humoral hypercalcemia of malignancy (HHM) [53].

Transforming growth factor-β (*TGF-β*) is a critical factor in the formation of bone metastases in breast cancer. TGF-β released by activated osteoclasts can further increase production of PTHrP through Smad-dependent and the p38 mitogen-activated protein kinase signaling pathway [54]. The elevated PTHrP increases RANKL to stimulate osteoclast formation and activity and promotes bone metastases. Subsequently, bone matrix factors are produced which in turn, influence cancer cells to maintain a vicious cycle. Expression of a TGF-beta ligand trap, which neutralizes TGF-beta1 and TGF-beta3 significantly, decreases osteolytic lesions in MDA-MB-231 breast cancer cells and also in vivo [55, 56]. Recently, Notch ligand Jagged1 which is an important mediator of bone metastases by activating the Notch pathway in bone cells could also be activated by TGF-β [57]. In addition, TGF-β can stimulate cyclooxygenase-2(COX-2) expression, leading to prostaglandin E2 (PGE2) production in MDA-MB-231 breast cancer cells [58]. The elevated PGE2 increases RANKL production through binding to its receptor EP4 on the surface of the osteoblasts, resulting in osteoclastogenesis [59].

A number of genes that are selectively upregulated in aggressive bone metastatic clones are identified by microarray analysis, including IL-11, chemokine receptor type 4 (CXCR4), CTGF and matrix metalloproteinase-1 (MMP-1) [60]. These genes are also contributed to bone metastases in breast cancer, and they are directly or indirectly regulated by TGF-β. TGF-β could also stabilize hypoxia-inducible factor-1 (HIF-1α) by inhibiting its degradation which promotes osteolysis by stimulating angiogenesis, osteoclastogenesis and inhibition of differentiation of osteoblasts. TGF-β1 biological signals are also produced by hypoxic metastatic cells [61–63]. Inhibition of TGF-β pathway could inhibit both bone and lung metastases in breast cancers [64–66]. Inhibitors targeting TGF-β pathway are mainly ligand traps, antisense oligonucleotides (ASO), small molecule receptor kinase inhibitors and peptide aptamers [66]. A pan-neutralizing anti-mouse TGF-β monoclonal antibody 1D11 reduces osteolytic lesions in vivo and vitro [68]. Type I receptor kinase inhibitor, Ki26894, YR-290 and a dual inhibitor of TβRI/II, LY2109761 also show their promising therapeutic roles in bone metastases in breast cancer. Although these targeted drugs result in a significant reduction in metastases in mouse models, it seems they do little on primary tumors. These data indicate a combined therapy may strengthen the efficacy of TGF-β-targeted drugs (Fig. 1).

Other factors produced by breast cancer cells can also induce osteoclastic activation such as IL family, IGFs

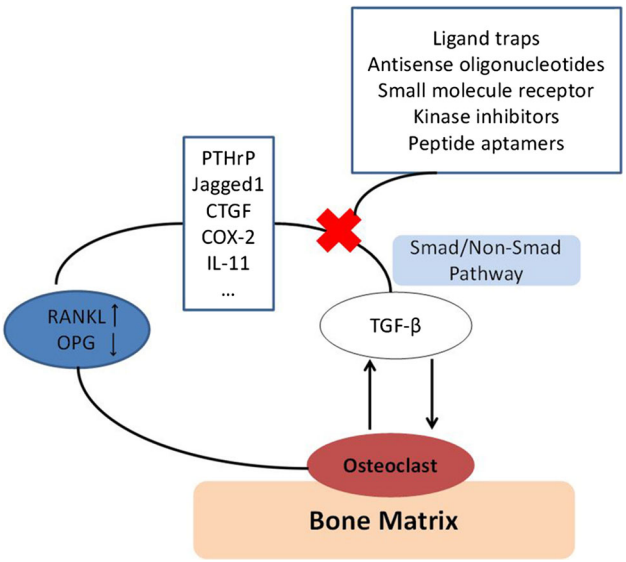

Fig. 1 Role of TGF-β in osteolytic breast cancer bone metastases. Drugs targeted TGF-β blocks TGF-β-regulated bone metastases

which are also implicated its role in proliferation of metastatic breast cancer cells in the bone [45, 46].

Common bone-targeted drugs both in prostate cancer and in breast cancer

In addition to drugs targeted to specific molecules in osteolytic or osteoblastic bone metastases, there are common bone-targeted therapies in prostate cancer and breast cancer. Currently, bisphosphonates (BPs) are the standard therapy for the prevention and treatment of malignant bone disease [69]. The second-generation nitrogen-containing BPs (N-BPs) (e.g., zoledronic acid, pamidronate) have better effects in reducing SREs compared with the first-generation BP compounds (e.g., clodronate) [70]. Zoledronic acid significantly reduces skeletal complications in breast cancer with bone metastases [71]. In addition, recent clinical trials indicated that adding zoledronic acid to adjuvant endocrine therapy improved disease-free survival (DFS) and overall survival (OS), especially in premenopausal women with early breast cancer and in women in established menopause at trial entry, indicating its potential antitumor effects [72]. Also, clinical trials indicate that adding zoledronic acid to adjuvant endocrine therapy improves bone mass density and prevents bone loss caused by endocrine therapy [73, 74]. Data with other bone-targeted agents are limited. Oral clodronate seemed to reduce distant metastasis in older postmenopausal women but no significance in OS and DFS in total population [75]. Also, no statistically significant differences in DFS or OS between the ibandronate and placebo-treated groups were seen. As in breast cancer, zoledronic acid also decreased SREs in hormone-refractory metastatic prostate cancer, although it did not improve OS and DFS [76]. However, pamidronate disodium failed to reduce bone pain or SREs compared with placebo [77]. Similarly, clodronate study did not demonstrate the efficacy for palliation of bone metastases symptoms in CPRC, although another trial of oral clodronate showed that OS was statistically significant in the men who received clodronate with long-term follow-up [78]. Recently, a meta-analysis compared the efficacy of BPs (zoledronic acid, ibandronate and pamidronate) in metastatic breast cancer, prostate cancer and multiple myeloma. As a result, zoledronic acid was clearly the best bisphosphonate for all three tumor types [79]. Another important bone-targeted drug is denosumab which is a fully humanized monoclonal antibody against RANKL approved by FDA for prevention of SREs. Recently, several clinical trials compared denosumab with zoledronic acid both in breast cancer and in prostate cancer and other solid tumors. Denosumab seems to be more effective in delaying or preventing SREs than zoledronic acid in patients with bone metastases from solid tumors potentially represents a novel treatment option for bone metastases [80, 81].

Conclusions and future perspectives

The cross-talk between bone microenvironment and different cancer cells activates and promotes various molecules and pathways, leading to the formation of different bone lesions, resulting in diverse clinical features.

Nowadays, targeted therapy is emerging as a new option in cancer treatment. Although the exact underlying mechanisms are not fully clarified in either osteoblastic or osteolytic bone lesions, it can provide therapy implications for bone metastases according to their unique molecules. In addition, although now common bone-targeted drugs such as BPs and denosumab play a main role in treating bone metastases, further research is needed to determine the optimal duration of treatment or treatment interval for patients who receive these medications for years. The potential benefits and adverse effects of these drugs should also be estimated according to more clinical trials. More specific targets based on cancer types may be also needed to improve current targeted therapies outcomes and reduce adverse effects. Further research into the molecular mechanisms of bone remodeling and bone metastases will provide more effective therapies with greater clinical efficacy than the therapies currently available.

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Conflict of interest The authors declare no conflict of interest.

References

1. Roodman GD. Mechanisms of bone metastasis. N Engl J Med. 2004;350:1655–64.
2. Mundy GR. Metastasis to bone: causes, consequences, and therapeutic opportunities. Nat Rev Cancer. 2002;2:584–93.
3. Guise T. Examining the metastatic niche: targeting the microenvironment. Semin Oncol. 2010;37(2):S2–14.
4. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20):6243s–9s.
5. Kataoka M, Kunisada T, Tanaka M, Takeda K, Itani S, Sugimoto Y, et al. Statistical analysis of prognostic factors for survival in patients with spinal metastases. Acta Med Okayama. 2012;66(3):213–9.
6. Kingsley LA, Fournier PG, Chirgwin JM, Guise TA. Molecular biology of bone metastases. Mol Cancer Ther. 2007;6:2609–17.
7. Lipton A, Cook R, Saad F, Major P, Garnero P, Terpos E, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. Cancer. 2008;113(1):193–201.
8. Sugiura H, Yamada K, Sugiura T, Hida T, Mitsudomi T. Predictors of survival in patients with bone metastasis of lung cancer. Clin Orthop Relat Res. 2008;466(3):729–36.
9. Drzymalski DM, Oh WK, Werner L, Regan MM, Kantoff P, Tuli S. Predictors of survival in patients with prostate cancer and spinal metastases. J Neurosurg Spine. 2010;13(6):789–94.

10. Yavas O, Hayran M, Ozisik Y. Factors affecting survival in breast cancer patients following bone metastases. Tumori. 2007;93(6):580–6.
11. Coleman RE. Bisphosphonates: clinical experience. Oncologist. 2004;9:14–27.
12. Coleman R, Brown J, Terpos E, Lipton A, Smith MR, Cook R, et al. Bone markers and their prognostic value in metastatic bone disease: clinical evidence and future directions. Cancer Treat Rev. 2008;34(7):629–39.
13. Coleman RE, Major P, Lipton A, Brown JE, Lee KA, Smith M, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. J Clin Oncol. 2005;23(22):4925–35.
14. Saad F, Lipton A. Bone-marker levels in patients with prostate cancer: potential correlations with outcomes. Curr Opin Support Palliat Care. 2010;4(3):127–34.
15. Brown JE, Cook RJ, Major P, Lipton A, Saad F, Smith M, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. J Natl Cancer Inst. 2005;97(1):59–69.
16. Ortiz A, Lin SH. Osteolytic and osteoblastic bone metastases: two extremes of the same spectrum? Recent Results Cancer Res. 2012;192:225–33.
17. Mohammad KS, Guise TA. Mechanisms of osteoblastic metastases: role of endothelin-1. Clin Orthop Relat Res. 2003;415:S67–74.
18. Granchi S, Brocchi S, Bonaccorsi L, Baldi E, Vinci MC, Forti G, et al. Endothelin-1 production by prostate cancer cell lines is up-regulated by factors involved in cancer progression and down-regulated by androgens. Prostate. 2001;49:267–77.
19. Clines GA, Guise TA. Molecular mechanisms and treatment of bone metastases. Expert Rev Mol Med. 2008;10:e7.
20. Clines GA, Mohammad KS, Bao Y, Stephens OW, Suva LJ, Shaughnessy JD Jr, et al. Dickkopf homolog 1 mediates endothelin-1-stimulated new bone formation. Mol Endocrinol. 2007;21:486–98.
21. Nelson JB, Chan-Tack K, Hedican SP, Magnuson SR, Opgenorth TJ, Bova GS, et al. Endothelin-1 production and decreased endothelin B receptor expression in advanced prostate cancer. Cancer Res. 1996;56:663–8.
22. Nelson J, Bagnato A, Battistini B, Nisen P. The endothelin axis: emerging role in cancer. Nat Rev Cancer. 2003;3:110–6.
23. Yin JJ, Mohammad KS, Käkönen SM, Harris S, Wu-Wong JR, Wessale JL, et al. A causal role for endothelin-1 in the pathogenesis of osteoblastic bone metastases. Proc Natl Acad Sci USA. 2003;100:10954–9.
24. Nelson JB, Love W, Chin JL, Saad F, Schulman CC, Sleep DJ, et al. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. Cancer. 2008;113:2478–87.
25. James ND, Caty A, Payne H, Borre M, Zonnenberg BA, Beuzeboc P, et al. Final safety and efficacy analysis of the specific endothelin A receptor antagonist zibotentan (ZD4054) in patients with metastatic castration-resistant prostate cancer and bone metastases who were pain-free or mildly symptomatic for pain: a double-blind, placebo-controlled, randomized Phase II trial. BJU Int. 2010;106(7):966–73.
26. Nelson JB, Fizazi K, Miller K, Higano C, Moul JW, Akaza H, et al. Phase 3, randomized, placebo-controlled study of zibotentan (ZD4054) in patients with castration-resistant prostate cancer metastatic to bone. Cancer. 2012;118(22):5709–18.
27. Fizazi KS, Higano CS, Nelson JB, Gleave M, Miller K, Morris T, et al. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2013;31(14):1740–7.
28. Day TF, Guo X, Garrett-Beal L, Yang Y. Wnt/β-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. Dev Cell. 2005;8:739–50.
29. Zi X, Guo Y, Simoneau AR, Hope C, Xie J, Holcombe RF, et al. Expression of Frzb/secreted Frizzled-related protein 3, a secreted Wnt antagonist, in human androgen-independent prostate cancer PC-3 cells suppresses tumor growth and cellular invasiveness. Cancer Res. 2005;65(21):9762–70.
30. Qiang YW, Chen Y, Stephens O, Brown N, Chen B, Epstein J, et al. Myeloma-derived Dickkopf-1 disrupts Wnt-regulated osteoprotegerin and RANKL production by osteoblasts: a potential mechanism underlying osteolytic bone lesions in multiple myeloma. Blood. 2008;112:196–207.
31. Hall CL, Bafico A, Dai J, Aaronson SA, Keller ET. Prostate cancer cells promote osteoblastic bone metastases through Wnts. Cancer Res. 2005;65:7554–60.
32. Menezes ME, Devine DJ, Shevde LA, Samant RS. Dickkopf1: a tumor suppressor or metastases promoter? Int J Cancer. 2012;130(7):1477–83.
33. Thudi NK, Martin CK, Murahari S, Shu ST, Lanigan LG, Werbeck JL, et al. Dickkopf-1 (DKK-1) stimulated prostate cancer growth and metastases and inhibited bone formation in osteoblastic bone metastases. Prostate. 2011;71(6):615–25.
34. Voorzanger-Rousselot N, Goehrig D, Journe F, Doriath V, Body JJ, Clézardin P, et al. Increased Dickkopf-1 expression in breast cancer bone metastases. Br J Cancer. 2007;97:964–70.
35. Schluter KD, Katzer C, Piper HM. An N-terminal PTHrP peptide fragment void of a PTH/PTHrP-receptor binding domain activates cardiac ET(A) receptors. Br J Pharmacol. 2001;132:427–32.
36. Guise TA, Mohammad KS, Clines G, Stebbins EG, Wong DH, Higgins LS, et al. Basic mechanisms responsible for osteolytic and osteoblastic bone metastases. Clin Cancer Res. 2006;12(Suppl 20):6213s–6s.
37. Baylink DJ, Finkelman RD, Mohan S. Growth factors to stimulate bone formation. J Bone Miner Res. 1993;8(Suppl 2):S565–72.
38. Autzen P, Robson CN, Bjartell A, Malcolm AJ, Johnson MI, Neal DE, et al. Bone morphogenetic protein 6 in skeletal metastases from prostate cancer and other common human malignancies. Br J Cancer. 1998;78:1219–23.
39. Feeley BT, Krenek L, Liu N, Hsu WK, Gamradt SC, Schwarz EM, et al. Overexpression of noggin inhibits BMP-mediated growth of osteolytic prostate cancer lesions. Bone. 2006;38:154–66.
40. Dai J, Kitagawa Y, Zhang J, Yao Z, Mizokami A, Cheng S, et al. Vascular endothelial growth factor contributes to the prostate cancer-induced osteoblast differentiation mediated by bone morphogenetic protein. Cancer Res. 2004;64:994–9.
41. Lee YC, Cheng CJ, Bilen MA, Lu JF, Satcher RL, Yu-Lee LY, et al. BMP4 promotes prostate tumor growth in bone through osteogenesis. Cancer Res. 2011;71(15):5194–203.
42. Haudenschild DR, Palmer SM, Moseley TA, You Z, Reddi AH. Bone morphogenetic protein (BMP)-6 signaling and BMP antagonist noggin in prostate cancer. Cancer Res. 2004;64(22):8276–84.
43. Virk MS, Alaee F, Petrigliano FA, Sugiyama O, Chatziioannou AF, Stout D, et al. Combined inhibition of the BMP pathway and the RANK-RANKL axis in a mixed lytic/blastic prostate cancer lesion. Bone. 2011;48(3):578–87.
44. Mehrotra M, Krane SM, Walters K, Pilbeam C. Differential regulation of platelet-derived growth factor stimulated migration and proliferation in osteoblastic cells. J Cell Biochem. 2004;93:741–52.
45. Bendre MS, Margulies AG, Walser B, Akel NS, Bhattacharrya S, Skinner RA, et al. Tumor derived interleukin-8 stimulates osteolysis independent of the receptor activator of nuclear factor-κB ligand pathway. Cancer Res. 2005;65:11001–9.
46. Kang Y, Siegel PM, Shu W, Drobnjak M, Kakonen SM, Cordón-Cardo C, et al. A multigenic program mediating breast cancer metastases to bone. Cancer Cell. 2003;3:537–49.
47. Guise TA. Parathyroid hormone-related protein and bone metastases. Cancer. 1997;80(8 Suppl):1572–80.
48. Guise TA, Yin JJ, Taylor SD, Kumagai Y, Dallas M, Boyce BF, et al. Evidence for causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis. J Clin Invest. 1996;98:1544–9.
49. Falzon M, Du P. Enhanced growth of MCF-7 breast cancer cells overexpressing parathyroid hormone-related peptide. Endocrinology. 2000;141:1882–92.
50. Isowa S, Shimo T, Ibaragi S, Kurio N, Okui T, Matsubara K, et al. PTHrP regulates angiogenesis and bone resorption via VEGF expression. Anticancer Res. 2010;30(7):2755–67.
51. Linforth R, Anderson N, Hoey R, Nolan T, Downey S, Brady G, et al. Coexpression of parathyroid hormone related protein and its receptor in early breast cancer predicts poor patient survival. Clin Cancer Res. 2002;8:3172–7.
52. Henderson MA, Danks JA, Slavin JL, Byrnes GB, Choong PF, Spillane JB, et al. Parathyroid hormone-related protein localization in breast cancers predict improved prognosis. Cancer Res. 2006;66:2250–6.
53. Saito H, Tsunenari T, Onuma E, Sato K, Ogata E, Yamada-Okabe H. Humanized monoclonal antibody against parathyroid hormone-related protein suppresses osteolytic bone metastases of human breast cancer cells derived from MDA-MB-231. Anticancer Res. 2005;25(6B):3817–23.
54. Kakonen SM, Selander KS, Chirgwin JM, Yin JJ, Burns S, Rankin WA, et al. Transforming growth factor-beta stimulates parathyroid hormone-related protein and osteolytic metastases via Smad and mitogen-activated protein kinase signaling pathways. J Biol Chem. 2002;277:24571–8.
55. Mourskaia AA, Dong Z, Ng S, Banville M, Zwaagstra JC, O'Connor-McCourt MD, et al. Transforming growth factor-β1 is the predominant isoform required for breast cancer cell outgrowth in bone. Oncogene. 2008;28(7):1005–15.
56. Chen YC, Sosnoski DM, Mastro AM. Breast cancer metastases to the bone: mechanisms of bone loss. Breast Cancer Res. 2010;12(6):215.
57. Sethi N, Dai X, Winter CG, Kang Y. Tumor-derived JAGGED1 promotes osteolytic bone metastases of breast cancer by engaging notch signaling in bone cells. Cancer Cell. 2011;19(2):192–205.
58. Hiraga T, Yoneda T. Stimulation of cyclooxygenase-2 expression by TGF-b enhances bone metastases in breast cancer. J Bone Miner Res. 2004;19:S129.
59. Ohshiba T, Miyaura C, Ito A. Role of prostaglandin E produced by osteoblasts in osteolysis due to bone metastases. Biochem Biophys Res Commun. 2003;300:957–64.
60. Buijs JT, Stayrook KR, Guise TA. TGF-β in the bone microenvironment: role in breast cancer metastases. Cancer Microenviron. 2011;4(3):261–81.
61. Maroni P, Matteucci E, Luzzati A, Perrucchini G, Bendinelli P, Desiderio MA. Nuclear co-localization and functional interaction of COX-2 and HIF-1α characterize bone metastases of human breast carcinoma. Breast Cancer Res Treat. 2011;129(2):433–50.
62. Hiraga T, Kizaka-Kondoh S, Hirota K, Hiraoka M, Yoneda T. Hypoxia and hypoxia-inducible factor-1 expression enhance osteolytic bone metastases of breast cancer. Cancer Res. 2007;67(9):4157–63.
63. McMahon S, Charbonneau M, Grandmont S, Richard DE, Dubois CM. Transforming growth factor beta1 induces hypoxia-inducible factor-1 stabilization through selective inhibition of PHD2 expression. J Biol Chem. 2006;281(34):24171–81.

64. Yin JJ, Selander K, Chirgwin JM, Dallas M, Grubbs BG, Wieser R, et al. TGF-β signaling blockade inhibits PTHrP secretion by breast cancer cells and bone metastases development. J Clin Invest. 1999;103:197–206.
65. Ganapathy V, Ge R, Grazioli A, Xie W, Banach-Petrosky W, Kang Y, et al. Targeting the transforming growth factor-beta pathway inhibits human basal-like breast cancer metastases. Mol Cancer. 2010;9:122.
66. Fang Y, Chen Y, Yu L, Zheng C, Qi Y, Li Z, et al. Inhibition of breast cancer metastases by a novel inhibitor of TGFβ receptor 1. J Natl Cancer Inst. 2013;105(1):47–58.
67. Connolly EC, Freimuth J, Akhurst RJ. Complexities of TGF-β targeted cancer therapy. Int J Biol Sci. 2012;8(7):964.
68. Drabsch Y, ten Dijke P. TGF-beta signaling in breast cancer cell invasion and bone metastases. J Mammary Gland Biol Neoplasia. 2011;16:97–108.
69. Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. J Clin Oncol. 2007;25(17):2464–72.
70. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol. 2008;19(3):420–32.
71. Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol. 2005;23(15):3314–21.
72. Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer. Clin Oncol. 2013;25(2):135–45.
73. Nuzzo F, Gallo C, Lastoria S, Di Maio M, Piccirillo MC, Gravina A, et al. Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: the randomized phase 3 HOBOE study. Ann Oncol. 2012;23(8):2027–33.
74. Llombart A, Frassoldati A, Paija O, Sleeboom HP, Jerusalem G, Mebis J, et al. Immediate administration of zoledronic acid reduces aromatase inhibitor–associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. Clin Breast Cancer. 2012;12(1):40–8.
75. Paterson AH, Anderson SJ, Lembersky BC, Fehrenbacher L, Falkson CI, King KM, et al. Oral clodronate for adjuvant treatment of operable breast cancer (national surgical adjuvant breast and bowel project protocol B-34): a multi-centre, placebo-controlled, randomised trial. Lancet Oncol. 2012;13(7):734–42.
76. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94(19):1458–68.
77. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. J Clin Oncol. 2003;21(23):4277–84.
78. Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes MR. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. Lancet Oncol. 2009;10(9):872–6.
79. Palmieri C, Fullarton JR, Brown J. Comparative efficacy of bisphosphonates in metastatic breast and prostate cancer and multiple myeloma: a mixed-treatment meta-analysis. Clin Cancer Res. 2013;19(24):6863–72.
80. Henry D, Vadhan-Raj S, Hirsh V, von Moos R, Hungria V, Costa L, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer. 2014;22(3):679–87.
81. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer. 2012;48(16):3082–92.