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Drug therapy for bone metastasis of malignant tumor: theory, progress, and potential

Minireview

Ji-Zheng TIAN, Ni-Na MA, Xiao LI, Kun SHANG, Bang-Wei CAO*

Cancer Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China

**Correspondence: oncology@ccmu.edu.cn*

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Bone is a common metastatic site of malignancies, caused by the complex interaction between tumor cells and the bone microenvironment. The complicated procedure covers multiple targets for therapeutic strategies against bone metastasis. At the present, only bisphosphonates and denosumab are currently approved for the prevention of skeletal-related events. But it is still ineffective for some patients, and none of them are proven to prolong the overall survival of patients with bone metastasis. Thus, new bone-modifying agents and therapeutic strategies are required. The review aimed to generalize the basic theory of bone metastasis and major put emphasis on the development of fundamental and potential target drugs in the behavior of bone metastasis. The summary of the drug development process helps to provide ideas for finding new and effective treatments for bone metastasis.

Key words: bone metastasis, bone microenvironment, bone-modifying agents, skeletal-related events

Bone is a major metastatic site of malignancies, such as breast cancer, prostate cancer, lung cancer, etc. [1]. Bone metastasis is divided into osteolytic metastasis with excessive bone resorption and osteoblastic metastasis with excessive bone formation. Bone metastasis can cause skeletal-related events (SREs), including bone radiotherapy, pathological fractures, spinal cord compression, surgery to bone, and hypercalcemia [2], which result in a poor prognosis and increase the economic burden.

The treatment of bone metastasis mainly includes bone modification drugs, radiotherapy, and surgery. The role of radiotherapy is mainly to relieve pain and increase strength, and the purpose of surgery is mainly to prevent disability. Bone-modifying drugs (BMAs) can be used throughout the entire process of treatment of bone metastasis to decrease the incidence of SREs. At present, just bisphosphonates and denosumab are currently approved for the prevention of SREs. But it is still vain for some patients, and not any of them are proved to prolong the overall survival of patients with bone metastasis. Thus, the development of new agents and new strategies are key to improve the treatment of bone metastasis. After decades of effort, the mechanism of bone metastasis has gradually been elucidated and drugs of different mechanisms are continuously emerging.

In this review, we would like to briefly summarize the basic theory of bone metastasis and put an emphasis on the key drugs and potential therapeutic interventions of bone metastasis.

The mechanism of bone metastasis

At present, the mechanism of bone metastasis is not clear. The "seed and soil" theory believed that the interaction between tumor cells and bone microenvironment plays an important role in tumor cells colonizing bone [3]. Emerging evidence has shown that primary tumor cells, bone marrow-derived myeloid cells (BMDCs) contribute to form the pre-metastatic niche (PMN) by releasing tumor-specific growth factors, inflammatory cytokines, chemokines, angiogenesis factors, etc. [4, 5], which is beneficial to the colonization and growth of tumor cells. Then, disseminated tumor cells (DTCs) in the bone matrix and bone marrow stroma interact with osteoclasts and osteoblasts resulting in bone destruction. Bone destruction produces bone-derived

cytokines such as insulin-like growth factors (IGFs) and transforming growth factor-beta (TGF-β), which are beneficial to the growth and invasion of tumor cells in bone tissue in turn. This is a "vicious circle" [6]. Therefore, the formation of the "vicious circle" is the key in the therapy of bone metastasis.

Bone normal physiology and bone metastasis pathology

Bone normal physiology depends on the dynamic balance between bone resorption by osteoclasts and bone formation by osteoblasts. Preclinical studies have confirmed several signaling pathways involved in osteogenesis and osteoclastogenesis (Figure 1). Metastatic tumor cells break the balance of osteoclasts and osteoblasts resulting in a "vicious circle". Herein, we reviewed the process of bone normal physiology and the "vicious circle" to provide a theoretical basis for the introduction of drug development.

Bone normal physiology. When bone is aged or damaged, osteoclast precursors differentiate into active osteoclasts via macrophage colony-stimulating factor (MCSF) and the receptor activator for nuclear factor-κ B ligand (RANKL) [7]. RANKL is a member of the tumor necrosis factor (TNF) family, produced by osteocytes, osteoblasts, and bone marrow stromal cells. RANKL binds to the receptor activator of nuclear factor-κB (RANK) on osteoclast precursors surface to trigger the activation of osteoclasts. Osteoprotegerin (OPG), a decoy receptor from osteoblasts, binds to RANKL and inhibits the RANK/RANKL signaling pathway, blocking excessive activation of osteoclasts [8–10] (Figure 1). Activated osteoclasts mediate bone resorption by expressing cathepsin K [11].

Bone resorption induces the release of factors like TGF-β, bone morphogenetic proteins (BMPs) from the bone matrix, which facilitate differentiation of mesenchymal stem cells (MSCs) into osteoblasts [12, 13]. Then, bone formation is activated. At the same time, osteocytes secrete sclerostin (SOST) and dickkopf1 (DKK1) to prevent excessive bone formation by blocking the WNT pathway [14] (Figure 1). Bone normal physiology depends on the balance between bone resorption and bone formation.

Pathology of osteolytic metastasis. Tumor-derived cytokines, such as IL-6, IL-8, IL-11, PTHrP, upregulate the expression of RANKL and downregulate the expression of OPG [15, 16]. Tumor cells also secrete MCSF [17] to promote osteoclasts differentiation and bone resorption. The activation of osteoclasts degrades the bone matrix leading to the release of numerous growth factors, such as TGF-β, IGFs, and Ca^{2+}, thus stimulating tumor cell proliferation [18]. On the other hand, tumor cells also inhibit osteoblast differentiation by secreting SOST and DKK1 [19]. All processes establish a "vicious circle" as described above (Figure 2).

Pathology of osteogenic metastasis. Osteogenic metastasis mainly occurs in advanced prostate cancer. The mechanism is not clear. Tumor-derived cytokines, such as endothelin-1 (ET-1) [20], BMPs, Wnt-family proteins (Wnts), TGF-β, are proved to promote osteoblast differentiation and osteogenesis (Figure 2). ET-1 downregulates

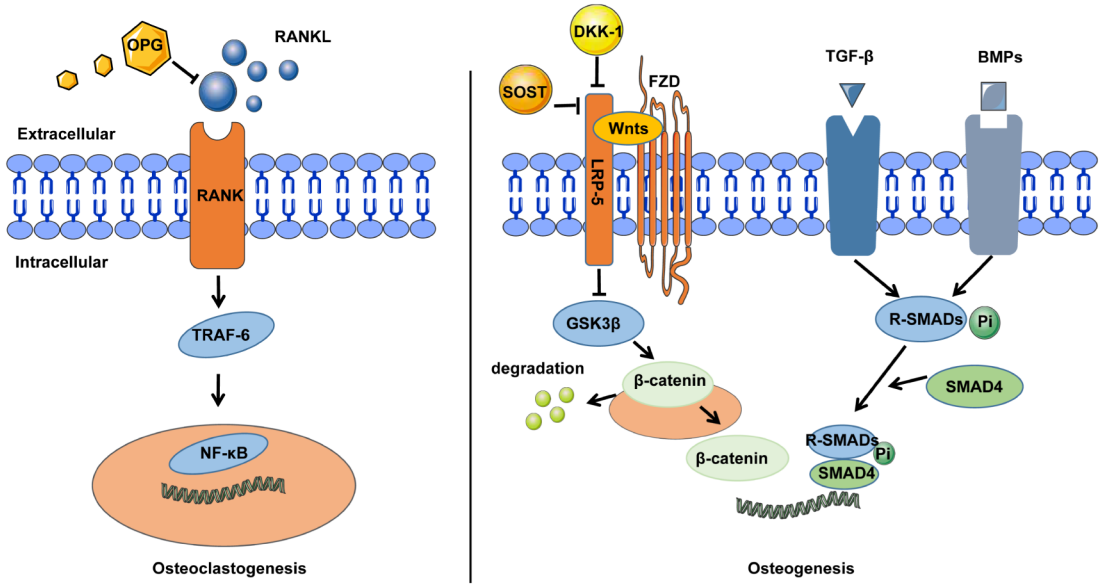

Figure 1. The signal pathway in osteoclastogenesis and osteogenesis. Abbreviations: OPG-osteoprotegerin; RANKL-receptor activator for nuclear factor-κ B ligand; RANK-receptor activator of nuclear factor-κB; TRAF-6-tumor necrosis factor receptor-associated factor 6; NF-κB-nuclear factor κB; SOST-sclerostin; DKK-1-dickkopf-1; Wnts-Wnt-family proteins; FZD-frizzled; LRP-5-low-density lipoprotein-related receptor-5; GSK3β-glycogen synthase kinase 3β; TGF-β-transforming growth factor-β; BMPs-bone morphogenetic proteins; SMAD4-mothers against decapentaplegic homolog 4; R-SMADs receptor-regulated Smads

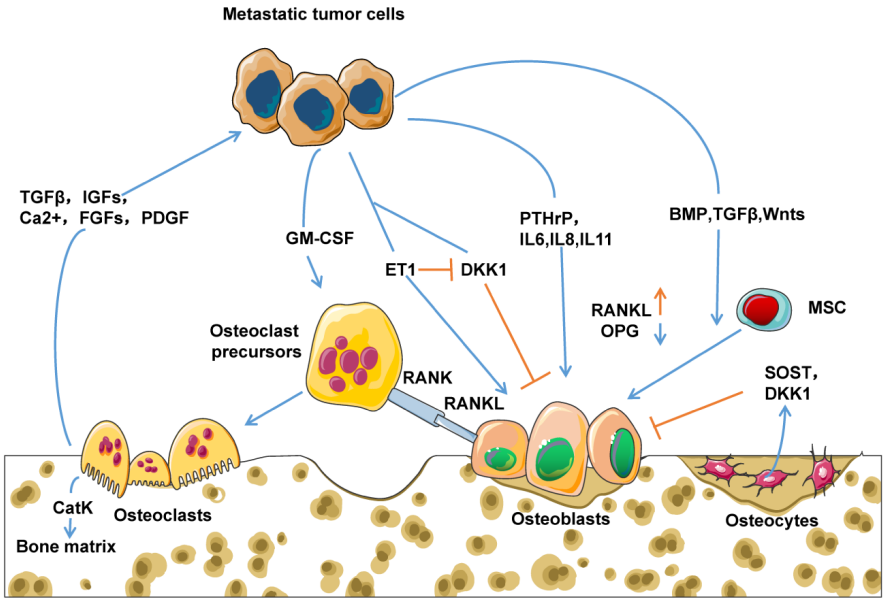

Figure 2. The development of bone metastasis and vicious cycle. Abbreviations: TGF-β-transforming growth factor-β; IGFs-insulin-like growth factors; FGFs-fibroblast growth factors; PDGF-platelet-derived growth factor; GM-CSF-granulocyte-macrophage colony-stimulating factor; ET-1-endothelin-1; PTHrP-parathyroid hormone-related protein; BMP-bone morphogenetic protein; TGF-β-transforming growth factor-β; Wnts-Wnt-family proteins; MSC-mesenchymal stem cell; OPG-osteoprotegerin; RANKL-receptor activator for nuclear factor-κ B ligand; RANK-receptor activator of nuclear factor-κB; SOST-sclerostin; DKK-1-dickkopf-1; CatK-cathepsin K

the autocrine production of DKK1 and promotes osteoblast differentiation via binding to the endothelin A receptor (ETR), activating Wnt signaling. ET-1 can also inhibit bone resorption to promote osteogenesis. BMPs and TGF-β promote osteoblast differentiation via the SMAD signaling pathway [21] (Figure 1).

The validated BMAs

The currently validated BMAs include bisphosphonates and denosumab, a RANKL inhibitor, both of which mainly act on osteoclasts. In the past decades, bisphosphonates and denosumab have elicited tremendous attention because of their success in achieving long-term durable responses. They have been proved to reduce and prolong the occurrence of SREs. Although there is no sufficient evidence to prove that bisphosphonates and denosumab can prolong the overall survival of patients, they are still the standard drugs of bone metastasis.

Bisphosphonates

Bisphosphonates have a very high affinity for hydroxyapatite crystals and can effectively suppress bone resorption by inhibiting hydroxyapatite breakdown. Based on this preclinical rationale, three generations of bisphosphonates entered the clinical development (Table 1). These results provided sufficient data support for the prevention of SREs [22–35].

The first generation is represented by Clodronate (CLO). Early reports of two controlled trials showed CLO could relieve bone pain in patients with breast cancer and prostate cancer [36, 37]. A double-blind controlled trial in patients with bone metastasis secondary to breast cancer who was randomized treated with CLO (1.6 g/d) or placebo demonstrated that the combined rate of all SREs was remarkably reduced (218.6 vs. 304.8/100 patient-years; $p<0.001$) [22]. Another randomized trial about metastatic breast cancer with bone involvement indicated that oral CLO (600 mg/bid) could significantly prolong the time to the first SRE than the control group ($p=0.015$) and the incidence of fractures was significantly reduced in the CLO group ($p=0.023$) [23].

Pamidronate is a second-generation agent. Combine data from two randomized controlled studies show Pamidronate (90 mg/3–4 w) was superior to placebo in patients with osteolytic bone metastasis from breast cancer [25]. The skeletal morbidity rate was lower in the Pamidronate group compared with placebo (2.4 vs. 3.7; $p<0.001$). The incidence of SREs was 51% in the Pamidronate group and 64% in the placebo group ($p<0.001$). Additionally, Pamidronate significantly increased median time to first SRE (12.7 vs. 7 months for placebo; $p<0.001$). Unfortunately, the data of head-to-head comparison with the first-generation drugs are missing, and no prospective randomized controlled study on prostate cancer has been designed, although Pamidronate is effective in the clinic.

Table 1. Clinical trials of bisphosphonates in patients with bone metastasis.

Agent	Patients	Dose	Results	Ref.
Clodronate				
vs. Placebo	Breast cancer	1.6 g/d	The combined rate of all morbid SREs ↓ (p<0.001)	[22]
vs. No-treatment	Breast cancer	800 mg bid po	the time to the first SRE → (p=0.015)	[23]
Pamidronate				
vs. Placebo	Breast cancer	60 mg/4 w	Cumulative number of SREs ↓ (p<0.01)	[24]
vs. Placebo	Breast cancer	90 mg/3-4 w	The skeletal morbidity rate ↓ (p<0.001) SREs ↓ (p<0.001) The median time to first SRE → (p<0.001)	[25]
Zoledronic acid				
vs. Placebo	Renal cell carcinoma	4 or 8 mg/3 w	The proportion of patients with an SRE↓ (p=0.015) The time to the first SRE → (p=0.006)	[26]
vs. Pamidronate	Breast cancer Multiple myeloma	4 mg/3-4 w vs. 90 mg/3-4 w	the overall risk of developing SREs ↓ (p=0.030) The risk of SREs in breast cancer ↓ (p=0.025)	[27]
vs. Placebo	Prostate cancer	4 mg/3 w	The annual incidence of SREs ↓ (p=0.005) The median time to the first SRE → (p=0.009) The ongoing risk of SREs ↓ (p=0.002)	[28]
vs. CLO	Prostate cancer	4 mg/m vs. 1.6 g/d	Bone progression-free survival ↑ (p=0.04)	[29]
vs. Placebo	Lung cancer and other solid tumors	4 or 8 mg/3 w	The median time to first SRE → (p=0.009) The annual incidence of SREs ↓ (p=0.012) The risk of developing a SRE ↓ (p=0.003)	[30]
Oral Ibandronate				
vs. Placebo	Breast cancer	20 or 50 mg/d	Skeletal morbidity period rate ↓ (p=0.024, p=0.037) The relative risk of SREs ↓ (p=0.009 and p=0.005)	[31]
vs. Placebo	Breast cancer	50 mg/d	Skeletal morbidity period rate ↓ (p=0.004) The risk of SREs ↓ (p=0.0001)	[32]
vs. ZOL	Breast cancer	50 mg/d vs. 4 mg/3-4 w	Annual rates of SREs non-inferiority	[33]
Ibandronate				
vs. Placebo	Colorectal carcinoma	6 mg/4 w	The proportion of patients with SREs ↓ (p=0.019) The time to first SRE → (p=0.009)	[34]
vs. Placebo	Breast cancer	6 mg/4 w	The proportion of patients with an SRE ↓ (p=0.027) Time to first SRE→ (p=0.007)	[35]

Notes: ↓ reduced, → prolonged. Abbreviations: SRE-skeletal-related event; COL-Clodronate; ZOL-Zoledronic acid

Zoledronic acid (ZOL), a third-generation agent, has demonstrated highly durable response rates of several large phase III studies involving patients with bone metastasis in advanced breast cancer, prostate cancer, renal cell carcinoma, lung cancer, and other solid tumors (Table 1). In a randomized double-blind multicenter trial of ZOL (4 or 8 mg) vs. Pamidronate (90 mg), ZOL (4 mg) significantly reduced the risk of SREs (p=0.025) compared with the Pamidronate group of patients with breast cancer [27]. The median time to first SRE was no statistically different between the two groups. However, subgroup analysis showed in breast cancer with hormonal therapy, ZOL (4 mg) prolonged the median time to the first SRE by 45 days (415 days vs. 370 days for Pamidronate; p=0.047). Additionally, another randomized placebo-controlled trial demonstrated the benefit of ZOL in the management of bone metastasis from advanced prostate cancer [38]. The result of 122 patients who completed a total of 24 months on study illustrated the median time to the first SRE was significantly prolonged in ZOL (4 mg) (488 days vs. 321 days for placebo; p=0.009). Based on the above research, ZOL is the most well-demonstrated bisphosphonate in prostate cancer and is also the most widely used bisphosphonate in clinical practice.

Ibandronate is another third-generation agent. In a non-inferiority phase 3 trial of bone metastasis from breast cancer, the findings could not reject the null hypothesis that oral Ibandronate (50 mg/d) was inferior to ZOL (4 mg/3–4 w). The notable result was that the incidence of renal toxic effects was 24% in the oral ibandronate group and 32% in the ZOL group [33]. Ibandronate was also evaluated in a randomized placebo-controlled pilot study, enrolling 73 patients with bone metastasis from colorectal carcinoma (CRC) [34]. Patients randomly received intravenous ibandronate (6 mg) every 4 weeks or a placebo. The results demonstrated that the proportion of patients with SREs was significantly reduced in the ibandronate group (39% vs. 78% with placebo; p=0.019) and the time to first SRE is extended by at least 6 months (median >279 vs. 93 days with placebo; p=0.009). One of our studies confirmed that the loading dose of Ibandronate (6 mg for three days) has certain advantages in reducing bone pain [39]. Although Ibandronate has not shaken the status of ZOL, it also provides a new option, especially in oral dosage forms.

Bisphosphonates are basic drugs recommended by guidelines for the treatment of bone metastasis. However, renal toxicity and the high incidence of osteonecrosis of the jaw (ONJ) have always been troubled issues in clinical practice. Therefore, we need drugs with few side effects.

RANKL inhibitor

Denosumab is the first anti-RANKL antibody approved for marketing. As a fully human anti-RANKL IgG2 antibody, Denosumab can suppress the activation of osteoclasts and prevent bone resorption by inhibiting the RANK/RANKL signaling pathway. Several studies confirmed the role of Denosumab in bone metastasis (Table 2).

In three presented randomized phase III studies, Denosumab (120 mg/4 w) was superior to ZOL (4 mg/4 w) in delaying time to first on-study SRE with advanced breast

Table 2. Current data of denosumab versus ZOL in patients with bone metastasis.

Patient population	Type of study	Results	Ref.
Breast cancer N=2046	RCT	Median time to first SRE: NoR vs. 26.4 months; p=0.01 Overall survival: HR 0.95; 95% CI:0.81 to 1.11; p=0.49	[40]
Prostate cancer N=1904	RCT	Median time to first SRE: 20.7 vs. 17.1 months; p=0.008 Overall survival: HR 1.03; 95% CI:0.91 to 1.17; p=0.65	[41]
MM N=1718	RCT	Median time to first SRE: 22.8 vs. 24.0 months; p=0.010 Overall survival: HR 0.90; 95% CI:0.70 to 1.16; p=0·41	[42]
Other solid tumors (Excluding BC and PC) or MM N=1776	RCT	Median time to first SRE: 20.6 vs 16.3 months; p=0.06 Overall survival: HR 0.95; 95% CI:0.83 to 1.08; p=0.43	[43]
Solid tumors (Except BC and PC) N=1597	Subgroup analysis of RCT	Median time to first SRE:21.4 vs. 15.4 months; p=0.017 Overall survival: HR 0.92; 95% CI:0.81 to 1.05; p=0.215	[44]
Solid tumors and MM N=5723	Combined analysis of 3 RCTs	Median time to first SRE: 27.66 vs. 19.45 months; p<0.001 Overall survival: HR 0.99; 95% CI:0.91 to 1.07; p=0.71	[45]
Gastrointestinal cancer and other rare cancer N=149	Retrospective study	Median time to SRE: 186 vs. 79 days; p=0.0053	[46]
Lung cancer N=411	Subgroup analysis of RCT	Overall survival: 8.9 vs. 7.7 months HR 0.80; 95% CI: 0.67 to 0.95; p=0.01	[47]
Non-squamous NSCLC N=103	Retrospective study	Overall survival: 21.4 vs. 12.7 months; p<0.01	[48]

Abbreviations: RCT-Randomized Controlled Trial; NoR-not reached; BC-Breast cancer; PC-Prostate cancer; MM-multiple myeloma; NSCLC-non-small cell lung cancer

cancer (p=0.01), prostate cancer (p=0.008), and multiple myeloma (p=0.010) [40, 42]. In another randomized phase III randomized involving patients with other advanced cancer (excluding breast and prostate cancer) and multiple myeloma, Denosumab was non-inferior to ZOL statistically (p=0.06) [43]. However, in a subgroup analysis of data from patients with solid tumors (except breast and prostate cancer), the median time to the first SRE was significantly prolonged in Denosumab (21.4 months vs. 15.4 months for ZOL; p=0.017) [44]. A combined analysis of three RCTs also confirmed that Denosumab (120 mg/4 w) can significantly prolong SREs in solid tumors and multiple myeloma (p<0.001) [45]. Evidence of Denosumab in gastrointestinal cancer was provided by a retrospective study in Japan, the result showed patients had benefited from Denosumab [46]. Unfortunately, Denosumab was not found overall survival better than ZOL above. Although a result of subgroup analysis from patients with lung cancer showed the median time of overall survival is prolonged by 1.2 months in Denosumab (8.9 vs. 7.7 months for ZOL; p=0.01) [47], and a retrospective study of non-squamous NSCLC observed the advantage of survival [48], more prospective data are needed to confirm the survival advantage.

On the other hand, clinical trials above had proved that denosumab was superior to ZOL in terms of renal toxicity. However, the incidence of ONJ is still high. Given that bisphosphonates and Denosumab are anti-bone resorptions, developing drugs with other mechanisms may prevent this trouble.

Other clinical trials of unapproved agents

Some other drugs are in clinical research, including anti-bone resorption agents and anti-bone formation agents. Although the results of preclinical studies are exciting, they have not brought adequate evidence for the treatment of bone metastasis. Some drugs are effective in the treatment of osteoporosis, but they cannot be confirmed in bone metastasis. The main reason is the difference in the bone microenvironment.

Cathepsin K inhibitors. Cathepsin K (CTSK) is a lysosomal cysteine protease secreted by activated osteoclasts, which could effectively mediate bone resorption by degrading type I collagen, type II collagen, and exciting matrix-metalloproteinase-9 (MMP-9) [49–51]. Therefore, CTSK inhibitors can prevent bone resorption theoretically. However, there are no approved agents for bone metastasis so far.

Odanacatib (ODN-MK-0822) was the first drug to show therapeutic effects in reducing the fracture risk of postmenopausal osteoporosis patients in the LOFT study but was associated with a high risk of cardiovascular events [52]. *In vitro* studies demonstrated that ODN-MK-0822 could inhibit invasion, migration and adhesion of human breast cancer cells [53] and decrease the mRNA expression of secreted pro-osteoclast factors [54]. In a randomized 2:1 study, Odanacatib (5 mg/d) suppressed uNTx equivalently to ZOL (4 mg/4 w) after 4 weeks of treatment in patients with bone metastasis of breast cancer [55]. There is no evidence of other CTSK inhibitors such as ONO-5334, AAE581, and MIV-711 in the treatment of bone metastasis.

c-Src inhibitors. c-Src is a non-receptor tyrosine kinase and is abundant in osteoclasts. Preclinical studies have proved c-Src plays an important role in cell proliferation, angiogenesis [56], and bone homeostasis [57]. c-Src affects the bone-resorbing activity of mature osteoclasts by boosting the rapid assembly and disassembly of the podosomes [58]. Therefore, the c-Src inhibitor may prevent osteoclast-mediated bone resorption.

On the basis of this preclinical rationale, four c-Src inhibitors, Dasatinib, Bosutinib, Vandetanib, and Saracatinib, were involved in clinical studies of bone metastasis. In phase I/II study of breast cancer bone metastasis, Dasatinib combined with zoledronic acid was proven to be well tolerated and had responses in patients with HR-positive [59]. However, in the SWOG S0622 study, either of the 2 dose schedules of Dasatinib was unsuccessful to control bone metastasis in metastatic breast cancer [60]. Similarly, another phase II study of Dasatinib with weekly Paclitaxel also showed ineffectiveness in MBC [61]. With respect to metastatic castration-resistance prostate cancer (CRPC), the READY study showed the Dasatinib (100 mg/d) group had no significant benefit in delaying median time to first SRE (not reached vs. 31.1 months for placebo; p=0.81) [62].

Other c-Src inhibitors, such as Bosutinib, Vandetanib, and Saracatinib, are also short of sufficient evidence of bone metastasis. Preclinical studies showed the ability of SKI-606 (Bosutinib) to block breast cancer and prostate cancer invasion, growth, and metastasis *in vitro* and *in vivo* [63–65]. Bosutinib could distinctly reduce tumor growth and lytic lesion areas in the bone by an animal model of prostate cancer [64]. Nevertheless, in a phase II study in patients with advanced breast cancer who pretreated with chemotherapy, Bosutinib did not change the level of bone resorption markers during the process of treatment [66]. In a randomized placebo-controlled study, Zamboney *et al.* showed that the addition of Vandetanib to Fulvestrant failed to prolong time to first SRE and change the biomarkers of bone turnover in hormone-receptor-positive metastatic breast cancer [67]. With respect to Saracatinib (AZD 0530), preclinical studies demonstrated Saracatinib (AZD 0530) could inhibit osteoclast formation effectively *in vitro* [68, 69] and prevent mice from developing severe osteolytic lesions *in vivo* studies [70]. The result of a phase I study showed Saracatinib significantly decreased the bone resorption markers of osteoclast activity in patients with advanced cancer [71]. However, further research showed that Saracatinib could not relieve bone pain effectively [72].

Integrin inhibitors. Integrins are heterodimeric cell surface receptors. Previous studies have established that integrins can mediate tumor cells' adhesion to the extracel-

lular matrix (ECM) [73, 74] and facilitate the proliferation and invasion of tumor cells [75]. Moreover, numerous studies have attempted to explain the role of αvβ3 in bone metastasis [76–78] and anti-αvβ3 therapy can reduce bone resorption by inhibiting osteoclast adhesion *in vitro* [79, 80]. Although initial enthusiasm for integrin inhibitors was generated from advanced cancers, the experience with integrin inhibitors in bone metastasis is less mature.

Cilengitide is a selective inhibitor of αvβ3 and αvβ5 integrins. A randomized phase II trial of metastatic castration-resistant prostate cancer patients was a failure of altering bone markers, so there were no further data about the bone disease [81].

MEDI-522 is another inhibitor of human αvβ3 integrin. Unfortunately, a phase II study in patients with metastatic androgen-independent prostate cancer who experienced MEDI-522 in combination with Docetaxel, Prednisone, and ZOL did not present the result of the incidence of SREs.

ATN-161 and PSK 1404, nonpeptide antagonist of αvβ3, could block bone metastasis and bone resorption in the animal model of breast cancer [82, 83].

The latest evidence showed that integrin alpha5 (ITGA5) is overexpressed in bone metastasis of breast cancer [84] and ITGA5 antibody (M200) decreased human osteoclast-mediated bone resorption *in vitro* [84]. We hope the effect of M200 could be confirmed *in vivo* and in clinical trials in the future.

DKK1 inhibitors and SOST inhibitors. Wnt signaling bone formation pathway has emerged as a crucial factor in bone formation [85, 86]. DKK1 and SOST was the antagonist of the Wnt signaling pathway as described above. Preclinical studies showed that inhibiting Dkk1 could prevent osteolytic disease in breast cancer and multiple myeloma [87, 88].

BHQ880 is a human anti-DKK1 monoclonal antibody. In a presented phase Ib study, BHQ880 in combination with zoledronic acid was effective in promoting bone mineral density (BMD) in MM [89]. A clinical trial of DKN-01, another new agent, is recruiting.

As regards SOST inhibitors, Romosozumab, Blosozumab, and BPS804 have been shown to result in disease responses in clinical trials of osteoporosis [90–92]. Unfortunately, researchers have not designed clinical trials on bone metastasis so far.

Potential drugs

Previous research has focused too much on bone resorption and reconstruction, which seems to ignore the role of the bone microenvironment. And the target is not accurate enough. Fortunately, scientists are constantly discovering new therapeutic targets, including bone-derived cytokines and new drug delivery systems, which have brought us positive signals.

Bone-derived growth factor inhibitors. Bone-derived cytokines such as IGFs and TGF-β and receptors played an important role in the "vicious circle" and epithelial-to-mesenchymal transition (EMT).

AZD3463, an IGF-1R inhibitor, suppresses bone metastasis of breast cancer via the PI3K-Akt pathway *in vitro*, especially when combined with ZOL [93].

TGFβR inhibitors ZL170 and SD208 reduce bone metastasis of breast cancer and prostate cancer via blocking the TGFβ/SMAD pathway [94, 95]. Given that growth factors are widely distributed in the human body, we need to develop more precise drugs to treat bone metastasis.

Targeting hypoxic microenvironment

The hypoxic microenvironment has emerging roles in the development of bone disease. Hypoxia plays a key role at all stages of bone metastasis. *In vitro* studies demonstrated that hypoxia promoted osteoclast formation by upregulating RANKL [96–98] and inhibited the differentiation of osteoblasts [99]. Hypoxia-inducible factor (HIF)-1 promoted the formation of PMN by regulating the expression of LOX [100, 101]. Targeting hypoxic microenvironment and HIF may a new treatment strategy for bone metastasis of malignant tumors.

CaSR inhibitors. The calcium-sensing receptor (CaSR) is a G-protein-coupled receptor. The function of CaSR is unequal in different tumors. CaSR is a protective receptor in colon cancer [102, 103]. Otherwise, previous studies have confirmed that overexpression of the CaSR promotes bone metastasis in several tumors such as breast cancer, prostate cancer, lung adenocarcinoma, and renal cell carcinoma [104–107]. CaSR might be a potential therapeutic target of preventing bone metastasis. NPS2143, a CaSR antagonist, was proven to reduce bone metastasis *in vitro* and animal models in renal cell carcinoma [106].

Nanodrugs and conjugate drugs. Many potential drugs have not reached effective concentrations to treat bone metastasis. To achieve the therapeutic concentration in the bone, the treatment of bone metastasis with the most effective and minimal systemic toxicity requires new treatment strategies. Nanoparticles encapsulate therapeutic drugs, protect them from degradation, and can bind to specific sites to improve efficacy. Another strategy is traditionally anti-tumor drugs such as Paclitaxel and Bortezomib specifically anchored to the bone by coupling with bisphosphonates [108].

Conclusion

At present, most studies on the mechanism of bone metastasis are mainly focused on breast and prostate cancer. There are many unclear mechanisms of bone metastasis because each tumor has its own characteristics. This is the main reason for the failure of many drugs. The drugs approved for the treatment of bone metastasis are limited. Anti-bone resorption therapy with bisphosphonates and denosumab

has improved the outlook for patients with bone metastasis in a variety of malignancies. Despite the benefit of this approach, many questions remain, such as not all patients respond to current agents, high incidence of osteonecrosis of the jaw, and no advantage in prolonging overall survival.

Therefore, further insight into the mechanisms of bone metastasis is needed, and new therapeutic strategies are required. With the continuous elucidation of tumor metastasis mechanism and innovation of anti-tumor therapy, we could focus our attention on the metastatic microenvironment, the formation of PMN, and the combined application of bone-targeted drugs and anti-tumor drugs, such as chemotherapy or immune checkpoint inhibitors. The therapy of bone metastasis will continue to be a challenge today and future.

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