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Progress in Diagnosis and Treatment Research of Bone Metastasis in Malignant Tumors

Abstract: - Bones are the most common target organs for metastasis in a variety of malignant tumors, including breast cancer and many other types of cancer that are not specifically listed, which are prone to bone metastasis. Bone metastasis can lead to various bone complications such as bone marrow compression and pathological fractures, significantly reducing patients' quality of life. This article provides a detailed overview of diagnostic methods for malignant tumor bone metastasis, their advantages and disadvantages, and comprehensively reviews the progress in treatment of bone metastasis, particularly focusing on targeted therapies.

Keywords: Bone metastasis ,diagnosis ,targeted therapy

1. INTRODUCTION

Bones are common targets for metastasis in various types of malignant tumors, especially for some cancer types such as breast cancer and other unspecified cancers, which are more prone to bone metastasis (Hofbauer et al.; Weilbaecher, Guise and McCauley).

Bone metastasis brings about various adverse consequences. Firstly, there is bone pain and neuropathic pain. Due to the decline in physical function and loss of autonomy caused by bone metastasis, the daily quality of life of patients with bone metastasis has been significantly negatively affected. For patients with established bone metastasis, initial symptoms typically manifest as bone pain, which may be initially confused with osteoarthritis but progresses over time to become persistent and severe pain(Mundy; Hofbauer et al.). In addition to somatic pain, proximity of bone to spinal cord and nerve roots can also lead to neuropathic pain (Coleman and Rubens). Another serious consequence of bone metastasis is pathological fractures, often caused by osteolytic changes in weight-bearing bones. When a pathological fracture occurs, the bone's healing ability is severely compromised, often requiring surgical intervention for treatment. This type of fracture is a highly destructive complication for cancer patients, as it not only exacerbates the deterioration of their quality of life but also further increases their mortality rate (Coleman and Rubens; Hofbauer et al.). In addition, bone metastasis can also lead to a critical metabolic complication known as hypercalcemia. This condition not only triggers emotional fluctuations, nausea, and gastrointestinal discomfort such as constipation but can also deteriorate further, manifesting as vomiting, dehydration, acute renal failure, and even fundamental changes in mental status, ultimately leading to coma and posing a life-threatening risk to patients (Van Poznak et al.) .

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However, in current medical practice, a unified and standardized process for the diagnosis and treatment of malignant bone metastases has not yet been established, leading to frequent misdiagnoses and mistreatments. Fortunately, with the continuous advancement of medical technology in recent years, the introduction of whole-body MRI technology and the emergence of novel targeted therapeutic drugs have provided important reference and solid foundation for precise diagnosis and effective treatment of bone metastasis diseases. This article systematically reviews current diagnostic methods and treatments for bone metastasis, aiming to summarize the advancements in its diagnosis and treatment.

2. THE DIAGNOSIS OF BONE METASTASIS

Accurate and timely diagnosis of metastatic bone disease is of paramount importance for patients. Traditionally, we rely on methods such as plain X-rays, CT scans, and radionuclide bone scans to detect bone metastases. However, these methods primarily focus on assessing the bone marrow's response to the cancer cell matrix rather than directly imaging the tumor itself, which somewhat limits early detection of bone metastases and accurate assessment of treatment response. Moreover, the accuracy of these methods in identifying metastatic lesions is less than 50% (Cook and Goh). Fortunately, with advancements in medical technology, highly sensitive imaging techniques have emerged, such as PET scans using various radioactive tracers and whole-body MRI, which have significantly improved the detection and assessment capabilities for metastatic bone disease (R. E. Coleman, P. I. Croucher, et al.). For asymptomatic patients, the diagnosis of bone metastases is often made incidentally during staging imaging or assessment of metastases in other parts of the body. For instance, a CT scan performed on a patient with liver metastases may unexpectedly reveal asymptomatic bone lesions. However, in certain unique scenarios, the symptoms or complications of bone metastases can actually present as the initial manifestation of a malignant tumo (R. E. Coleman, P. I. Croucher, et al.).

2.1 Bone scintigraphy

Bone scintigraphy technology identifies bone metastases by capturing the accumulation of radioactive tracers in bones when osteoblast activity increases near the site of metastasis (Shen et al.). However, as demonstrated in studies on prostate cancer patients, this technique has limitations in detecting bone metastasis lesions, with sensitivity and specificity of only 59% and 75% respectively, and the detected abnormal areas do not always directly correspond to bone metastases (Shen et al.). Despite these shortcomings, bone scintigraphy remains the preferred initial diagnostic tool for patients with suspected bone metastases in clinical settings, but this choice is not applicable to all cases, particularly those with predominantly osteolytic lesions such as renal cell carcinoma, multiple myeloma, and thyroid cancer, where the uptake of radioactive tracers is often low.

2.2 CT imaging

Before CT scanning technology can clearly reveal the internal condition of bones, significant structural changes often occur, including bone destruction and the formation of new bone. These changes serve as important indicators of disease progression, but their presence also suggests that the condition may have already advanced to a certain stage. Adding to the complexity, when tumor cells are concealed within calcified bones, particularly in fatty marrow regions, CT scanning faces considerable challenges in accurately identifying these tumor cells. Despite these difficulties, CT scanning still demonstrates its unique value in the diagnosis of cancer-induced bone

metastases. According to the thorough research conducted by scholars such as Yang, CT scanning exhibits a relatively high sensitivity of 73% in detecting bone metastases caused by cancer. This implies that in most cases, CT scanning can identify the presence of bone metastases with a fair degree of accuracy, allowing patients to gain valuable time for treatment. Furthermore, its specificity is also as high as 95%, further proving the accuracy and reliability of CT scanning in distinguishing normal bone from bone metastasis lesions. Nevertheless, a notable limitation of CT imaging lies in the lack of a stable and reliable pathological standard for accurately interpreting CT scan results. Combined with bone scintigraphy, CT can provide more comprehensive diagnostic information for bone metastases.

2.3 Whole-body imaging

Bone scintigraphy and CT imaging both have deficiencies in sensitivity and specificity. In light of these limitations, modern imaging techniques such as MRI and PET-CT combined imaging are increasingly favored and recommended as alternative diagnostic methods to more accurately detect bone metastases (Cornford et al.; Crawford et al.). The PET isotope fluorine-18 sodium fluoride (18F-NaF) is a bone turnover-specific radiotracer that potentially offers the highest sensitivity (R. E. Coleman, P. I. Croucher, et al.). In PET registration trials among patients with prostate cancer, breast cancer, lung cancer, and other cancers, it was found that over 40% of patients experienced a significant shift from non-treatment to treatment strategies following PET imaging with fluorine-18 sodium fluoride isotopes, leading to substantial therapeutic management changes (Hillner et al.). PET-CT utilizes radiopharmaceuticals such as choline or fluorothymidine, and fluorodeoxyglucose for metabolic imaging. Compared to CT or bone scintigraphy, PET-CT exhibits fewer uncertainties and false positives, rendering it more sensitive in detecting metastases. Other radiotracers, such as prostate-specific membrane antigen (PSMA) labeled with gallium, show approximately 23% higher detection rates than traditional imaging modalities in cases of biochemical recurrence post-prostatectomy(Calais et al.; Hofman et al.).

Compared to bone scintigraphy and CT, whole-body MRI has demonstrated higher sensitivity in detecting bone metastases, with diagnostic performance comparable to that of choline PET/CT (Crawford et al.).Whole-body MRI, including visual assessment of imaging features, combined with corresponding apparent diffusion coefficient values and measurement of bone lesion fat, improves diagnostic accuracy compared to the potential anomalies detected using only morphological features for the detection of bone metastases.

2.4 Histological examination

When imaging studies reveal bone lesions or other clear metastases, a biopsy may not be necessary. However, if there are few lesions or the imaging findings are inconclusive, histological assessment is strongly recommended to aid in diagnosis. Metastases confined solely to the bone can be challenging to detect with imaging alone, a phenomenon commonly observed in breast and prostate cancers. Whole-body MRI, including visual assessment of imaging features combined with corresponding apparent diffusion coefficient (ADC) values and fat quantification of bone lesions, improves diagnostic accuracy compared to using morphological criteria alone to detect potential bone metastases. Histological evaluation can also indicate the primary site of the tumor. Biopsy of suspected areas, guided by CT imaging and followed by pathological evaluation, is a complex process best performed by experts familiar with bone biopsy techniques. A biopsy not only corroborates imaging findings but

also provides an opportunity to reassess tumor-specific biomarkers, which may help guide subsequent treatment strategies.

2.5 The detection of biomarkers

The abnormality in bone remodeling stems fundamentally from the disruption of the delicate balance between bone formation and resorption. In evaluating this complex physiological phenomenon, the R.Coleman research team has made a significant breakthrough by discovering a non-invasive method—detecting specific biochemical markers present in blood or urine samples to gain insights into the health status of bone remodeling.

These crucial biochemical markers serve as mirrors, reflecting the subtle changes occurring within the bone. Among them, one category of markers arises from the active process of bone resorption. They are the hallmark fragments released during the degradation of type I collagen, particularly the amino-terminal and carboxy-terminal cross-linking telopeptides. The presence of these peptides directly reflects the rate and extent of bone breakdown. On the other hand, to understand how bones are rebuilt, we turn our attention to another category of markers—the precollagen fragments incorporated into the newly formed bone matrix during bone formation. Notably, the N-terminal propeptide (P1NP) and C-terminal propeptide of type I procollagen are direct evidence of new bone generation, and changes in their levels can reveal the degree of bone formation activity.

Additionally, an indicator that cannot be overlooked is bone alkaline phosphatase, a crucial enzyme secreted by osteoblasts that plays a vital role in the mineralization process of bones. By measuring its concentration, we can gain further insights into the efficiency and status of bone mineralization. These biochemical markers collectively function as a barometer of bone metabolism, accurately reflecting the relative rates of bone resorption and formation, providing us with invaluable health information. However, it is essential to clarify that while these markers are highly valuable in assessing bone metabolic status, they do not directly pinpoint the location of specific lesions. Therefore, in clinical applications, it is necessary to combine them with other diagnostic tools for comprehensive judgment. Although elevated levels of certain markers may support the diagnostic hypothesis of bone metastases, their generally low sensitivity and specificity preclude their use as definitive diagnostic criteria. Nevertheless, the detection of biomarkers remains a valuable reference for guiding the formulation of subsequent treatment plans and assessing disease prognosis.

3. TREATMENT OF BONE METASTASIS

The primary goal of treatment for bone metastases is to reduce the incidence of bone-related complications. The selection of treatment options requires comprehensive consideration of the patient's presence of extraskeletal metastases, the specific type of tumor, and the severity of bone lesions. Currently, the treatment of bone metastases encompasses various approaches, including surgical resection of lesions, radiotherapy, systemic treatment with cytotoxic anticancer drugs (chemotherapy) or hormonal drugs, as well as emerging targeted therapies. In the following discussion, we will delve into the latest advancements in the field of bone metastases treatment, particularly the detailed application of targeted therapies. Furthermore, based on current research findings, we will elaborate on our understanding of the mechanisms underlying the progression of bone metastases.

3.1 Surgical resection

For resectable bone metastases, surgical treatment should be considered first. Surgical resection can effectively alleviate pain and extend patient survival. For instance, in the case of cervical cancer with bone metastases, surgical resection has been shown to reduce pain and prolong survival, with some patients surviving up to 39 months (Zhao et al.; Pasricha et al.).

3.2 Radiation therapy

Pain caused by bone metastases can be significantly alleviated through radiation therapy. The specific methods of radiation therapy are diverse, including external beam radiation therapy (EBRT), its advanced form - stereotactic body radiation therapy (SBRT), and radionuclide therapy. When selecting the type of radiation therapy and determining the optimal timing, it is crucial to comprehensively consider the patient's tumor histology, prognosis, as well as the specific location and severity of bone metastases (Shiloh and Krishnan).

3.2.1 External beam radiation therapy

External Beam Radiation Therapy (EBRT) has been widely recognized as an effective method for treating pain caused by bone metastases. Multiple prospective clinical trials have revealed that most patients experience similar therapeutic benefits from both single-fraction and multiple-fraction radiation therapy. However, it is noteworthy that due to the consistently high re-treatment rates observed after single-fraction therapy in numerous studies, for patients with a smaller number of metastatic lesions and good prognosis, a relatively longer course of EBRT treatment may be a more suitable option to achieve a more durable therapeutic effect (Majumder et al.).

3.2.2 Stereotactic body radiation therapy

EBRT is a conventional treatment for painful bone metastases, but its application is limited by the potential harm to surrounding healthy tissues (such as the spinal cord), which restricts the upper limit of radiation dose. To overcome this limitation, Stereotactic Body Radiation Therapy (SBRT), an advanced technology of EBRT, emerged as a solution. SBRT provides a highly focused form of radiation that can enhance therapeutic effects while effectively protecting surrounding healthy tissues (as pointed out by Shiloh and Krishnan). Multiple studies have shown that SBRT achieves a local control rate of 80% to 90% within one year. The application scenarios of SBRT mainly focus on three types of cases: firstly, patients with low metastatic tumors; secondly, patients requiring retreatment; and lastly, patients with tissue types that exhibit radioresistance, such as renal cell carcinoma or melanoma.

3.2.3 Radiopharmaceuticals

Although External Beam Radiation Therapy (EBRT) has achieved remarkable success in alleviating local pain caused by bone metastases, due to the fact that bone metastasis patients often suffer from systemic diseases, relying solely on EBRT is often insufficient to achieve the desired therapeutic effect. In this context, radiopharmaceuticals such as the α-emitter Radium-223 (223Ra) and β-emitters Strontium-89 (89Sr) and Samarium-153 (153Sm) have emerged as promising tools for managing bone pain, particularly in patients with castration-resistant metastatic prostate cancer. It is noteworthy that while both β-emitters, 89Sr and 153Sm, have been approved by the Food and Drug Administration (FDA) for the treatment of pain related to bone metastases,

they may cause side effects such as bone marrow suppression. In contrast, Samarium-153 and Strontium-89 have lower linear energy transfer and limited penetration depths of approximately 3-8 millimeters, which while effective in targeting bone tissue, can also lead to more severe bone damage, thereby limiting their ability to be combined with other treatment modalities (as noted by Coleman). The α-emitter, Radium-223 (223Ra), stands out as it has been approved by the FDA for the treatment of symptomatic bone metastases in castration-resistant prostate cancer with no known visceral metastases. It not only improves patients' quality of life and overall survival rates but also avoids the risk of bone marrow suppression, thereby opening up new avenues for the treatment of bone metastases(Shiloh and Krishnan).

3.3 Cytotoxic antineoplastic drugs

Cytotoxic antineoplastic drugs, known as chemotherapy agents, are typically used to reduce or eliminate solid tumors and hematologic malignancies, often in combination with other cancer therapies such as surgery, radiation therapy, targeted therapy, and immunotherapy, for the treatment of malignant tumors(Schirrmacher). Different types of chemotherapy drugs inhibit tumor cell proliferation and metastasis through various mechanisms. Common chemotherapy agents target cell cycle control, DNA replication and transcription, cellular metabolism, or hormone response. For example, alkylating agents can directly induce DNA strand breaks, incorrect base pairing, or DNA cross-linking, thereby preventing cell division; topoisomerase inhibitors block normal DNA breakage and ligation during the transcription process; platinum-based chemotherapeutic agents can directly induce interstrand and intrastrand DNA cross-links as well as DNA-protein cross-links to inhibit DNA function; antitumor antibiotics can disrupt DNA structure during RNA synthesis, affecting cell proliferation; plant alkaloids target the cell cycle by blocking cell division in the S or M phase; antimetabolites can impede the normal function of enzymes required for metabolism and protein synthesis; taxanes interfere to prevent cell division(Pomeroy et al.; Bax et al.; Moreira-Pais, Ferreira and Gil da Costa; Leitsch; Omar et al.; Sun et al.). However, chemotherapy is associated with a range of side effects, including nausea, hair loss, mucositis, vomiting, anemia, neuropathy, cognitive impairment, heart failure, weight loss, muscle and bone loss, fatigue, and severe renal dysfunction(Hain and Waning; Schirrmacher; Oun, Moussa and Wheate).

3.4 Systemic treatment with endocrine therapy drugs

The most common type of cancer associated with bone metastases is breast cancer, and endocrine therapy primarily focuses on this type as well as another significantly related cancer—specifically, those tumors that are highly hormone-sensitive. Among cancers, especially in approximately two-thirds of cases, there is an overexpression of estrogen receptors, a characteristic that makes them hormone-dependent tumors. As a result, endocrine therapy plays a pivotal role in the treatment of these cancers. There are three main classes of endocrine therapy drugs for breast cancer: anti-estrogens (tamoxifen, fulvestrant, toremifene), aromatase inhibitors (anastrozole, letrozole, exemestane), and progesterone receptor antagonists (mifepristone, megestrol acetate). Different subtypes of breast cancer respond differently to these therapies. In premenopausal patients, daily 20 mg tamoxifen is the standard endocrine treatment, significantly reducing the five-year recurrence rate and breast cancer mortality. Addition of ovarian suppression agents or aromatase inhibitors can enhance therapeutic efficacy(Tamura; Hiscox et al.; Hanker, Sudhan and Arteaga; Harbeck and Gnant).

In prostate cancer, the primary approach involves reducing the levels of androgens produced in the testes, a method known as androgen deprivation therapy (ADT). Testicular removal results in permanent androgen suppression, but its use is limited. Therefore, pharmacological castration is the mainstay of endocrine therapy. There is a wide variety of therapeutic drugs for prostate cancer, each with its unique mechanism of action. They primarily operate in the following aspects: firstly, inhibiting the production of androgens by the testicles, which includes the use of gonadotropin-releasing hormone agonists and gonadotropin-releasing hormone antagonists; secondly, reducing the amount of androgens secreted by the adrenal glands, which can be achieved through drugs such as abiraterone or ketoconazole; thirdly, blocking the pathway of androgen action, which is further divided into first-generation drugs like flutamide, bicalutamide, and nilutamide, as well as more advanced second-generation drugs such as enzalutamide, apalutamide, and darolutamide; finally, there are other methods of inhibiting androgens, such as using estrogens for treatment (Rachner et al.; Kahn et al.).

Abiraterone, as a non-reversible inhibitor of androgen biosynthesis, functions by effectively reducing the amount of androgens released by the adrenal glands (as indicated by the research of O'Donnell et al.). Solid data from two pivotal Phase III clinical trials, COU-AA-301 and COU-AA-302, conclusively demonstrate that abiraterone significantly improves overall survival and bone health outcomes for patients, regardless of whether they are in the early or late stages of treatment (findings by Gartrell and Saad). Notably, in the treatment of metastatic bone disease, abiraterone employs a systemic approach that not only directly inhibits bone resorption but also stimulates bone anabolic activity (research by Iuliani et al.). Additionally, another noteworthy inhibitor is the androgen receptor antagonist enzalutamide, which also shows promising potential for widespread application. Enzalutamide significantly reduced the risk of death and improved skeletal outcomes in two Phase III trials.

However, with these endocrine therapies, nearly all patients eventually develop secondary resistance.

3.5 Targeted therapy

3.5.1 Inhibiting bone resorption by targeting osteoclasts

3.5.1.1 Bisphosphonates

Bisphosphonates mimic pyrophosphate, with a structure containing P-C-P and a variable R chain. Depending on whether the R group contains nitrogen, they can be divided into two categories: nitrogen-containing bisphosphonates (such as zoledronic acid) inhibit osteoclast survival enzymes, while non-nitrogenous bisphosphonates (such as clodronate) convert toxic substances to induce apoptosis. Bisphosphonates are taken up by osteoclasts, interfering with their biochemical processes and leading to apoptosis, particularly with non-nitrogenous bisphosphonates triggering this through the generation of toxic substances. Bisphosphonates have a long biological half-life, with the effects of a single dose lasting for several years.

The use of bisphosphonates as bone-targeted drugs in the treatment of breast cancer bone metastasis has shown significant therapeutic efficacy and has become a first-line treatment. Completed randomized placebo-controlled clinical trials have conclusively demonstrated the clinical effectiveness of oral clodronate and ibandronate sodium, as well as intravenous pamidronate disodium, ibandronate, and zoledronic acid preparations (Clézardin et al.). The first intravenously administered bisphosphonate to be systematically evaluated was pamidronate, which has

demonstrated significant clinical efficacy in improving quality of life, reducing skeletal morbidity, and alleviating pain in breast cancer patients(Lipton et al.). Zoledronic acid, as the most effective bisphosphonate drug at present, has been the first choice in global clinical practice for more than a decade. More importantly, it has shown more significant efficacy in preventing skeletal-related events associated with bone metastases compared to intravenous pamidronate disodium and oral ibandronate sodium (Barrett-Lee et al.).

Bisphosphonates alleviate bone lesions in advanced prostate cancer, reduce bone pain, and lower bone resorption markers. They also prevent bone loss during cancer treatment, especially in long-term cancer survivors who are at higher risk of developing osteoporosis. Premenopausal women can regularly use zoledronic acid to prevent bone loss. Zoledronic acid aids in the treatment of early-stage cancer by inhibiting tumor cell proliferation and diffusion, with bisphosphonates exhibiting multiple direct and indirect anti-cancer mechanisms. However, high doses of bisphosphonates increase the risk of osteonecrosis of the jaw, limiting their application in bone metastasis. Enhanced dental care, good oral hygiene, and timely clinical treatment can prevent osteonecrosis of the jaw.

3.5.1.2 Denosuma

In hereditary breast cancer, BRCA1 mutations play a crucial role in carcinogenesis, with the RANK/RANKL pathway being essential. BRCA1 mutations increase the number of cancer stem cells, whose proliferation strongly depends on the RANKL/RANK pathway (Rao et al.).

Denosumab is a human-designed protein synthesized to inhibit the interaction between RANK and RANKL. Recombinant proteins are fused with human IgG1-Fc and the cysteine-rich domain (CRD) of OPG or RANK for specific functions. Fc-OPG and RANK-Fc significantly inhibit bone resorption in models. Denosumab outperforms zoledronic acid in preventing cancer-related skeletal events, has a short half-life, is administered through subcutaneous injection, and can also prevent bone loss caused by cancer treatment.

3.5.1.3 Novel anti-resorptive agents

3.5.1.3.1 LGR4/RANKL and small molecule RANKL inhibitors

Recently, G protein-coupled receptor 4 (LGR4) has been found to negatively regulate osteoclast differentiation. LGR4 inhibits the classical RANK signaling pathway by competing with RANK for binding to RANKL(Luo et al.). Studies on osteoporosis animal models have explored the binding of LGR4-ECD to RANKL, resulting in increased bone mass and inhibited osteoclast differentiation (Luo et al.). This binding has no significant effect on normal mice but shows potential therapeutic value for conditions such as bone defects. LGR4-ECD may antagonize excessive RANKL in bone diseases. Animal model evaluations of the AS2676293 inhibitor show that oral administration can inhibit osteolytic lesions in cancer (Nakai et al.). In vitro, AS2676293 inhibits osteoclast formation. This drug is currently in the preclinical development stage.

3.5.1.3.2 Inhibitor of tissue protease K

Cathepsin K is highly expressed in osteoclasts and promotes bone resorption. Its inhibitors (such as AFG-495) have been shown to reduce tumor burden and inhibit bone damage in animal models of cancer bone metastasis, helping to understand its mechanism (Duong's team). AFG-495 blocks breast cancer invasion in vitro but does not inhibit tumor growth in vivo, demonstrating its dual therapeutic potential: reducing bone resorption and

lightening tumor burden (Le Gall). In clinical trials, odanacatib (similar to L-235) reduced bone resorption markers within 4 weeks (Jensen). For postmenopausal women with osteoporosis, it effectively increased bone density and inhibited bone resorption (Boucharaba). However, concerns over cardiovascular safety led to the discontinuation of its development, and a Phase III trial (NCT00692458) evaluating its efficacy in reducing the risk of breast cancer bone metastasis was cancelled for unknown reasons.

3.5.1.3.3 The target of mammalian rapamycin inhibitors

RANKL and M-CSF enhance osteoclast activity through the mTOR signaling pathway. The mTOR inhibitors rapamycin and everolimus inhibit bone resorption and block osteoclast differentiation in an ovariectomy-induced bone loss model. Everolimus and temsirolimus can be used to treat advanced breast cancer and renal cell carcinoma, inhibiting related osteolysis. The combination therapy of everolimus and exemestane has been approved for the treatment of HER2-negative advanced breast cancer, prolonging progression-free survival (Baselga et al.) .During treatment with exemestane, bone marker levels increase; however, when combined with everolimus, bone marker levels decrease (M. Gnant et al.) .In summary, the combination of everolimus and exemestane may slow the progression of bone disease by inhibiting the bone turnover associated with exemestane monotherapy.

3.5.1.3.4 SRC is a non-receptor tyrosine kinase inhibitor

SRC is a member of the non-receptor tyrosine kinase family, capable of interacting with multiple protein tyrosine kinase receptors, integrins, and G-protein coupled receptors. Protein levels of SRC are higher in platelets, osteoclasts, and neurons compared to other cells(Roskoski) . SRC phosphorylates and regulates osteoclast cytoskeletal proteins, enabling osteoclasts to adhere, spread on bone surfaces, and promote bone resorption. Additionally, SRC activates the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway, thereby promoting osteoclast survival (Sousa and Clézardin) .The most prominent phenotype observed in SRC gene knockout mice is osteoporosis (Roskoski) .Saracatinib, dasatinib, and bosutinib (three SRC inhibitors) have entered clinical trials, but the results have been less favorable than expected (Sousa and Clézardin).

3.5.1.3.5 RON receptor tyrosine kinase inhibitor

RON is a receptor tyrosine kinase expressed in osteoclasts (discovered by the Andrade team). In animal experiments simulating breast cancer bone metastasis, RON tyrosine kinase inhibitors (such as BMS-777607/ASLAN002) successfully inhibited the formation of osteolytic lesions (studied by Andrade et al.). In addition, the results of Phase I clinical trials in postmenopausal patients with advanced cancer showed that after 4 weeks of treatment with BMS-777607/ASLAN002 (NCT01721148), the bone resorption level of patients was significantly reduced.

3.5.1.3.6 C-MET and VEGFR2 receptor tyrosine kinase inhibitors

Receptor tyrosine kinase (cMET) and VEGFR signaling pathways promote tumor development and progression by activating multiple pathways, including SRC, PI3K/AKT/mTOR, and MAP kinase (Lee and Smith)。 Cabozantinib and TAS-115 are dual tyrosine kinase inhibitors targeting VEGFR2 and c-MET. Preclinical and clinical studies have demonstrated that cabozantinib inhibits osteoclast-mediated bone resorption, osteoclast

differentiation, and enhances osteoblast proliferation (Fioramonti et al.) .An animal model of prostate cancer demonstrated that cabozantinib reduces osteoblastic lesions and skeletal tumor burden. Concurrently, TAS-115 inhibits bone destruction and the formation of bone metastasis in human PC-3 prostate cancer (Lee et al.; Watanabe et al.) .Despite no improvement in clinical trials phase II and III for the treatment of prostate cancer, cabozantinib failed to demonstrate an increase in overall survival rate, leading to its discontinuation in prostate cancer development. However, cabozantinib was unexpectedly found to have a direct impact on bone cell function and bone marrow suppression. Currently, cabozantinib has been approved for the treatment of advanced renal cell carcinoma patients following anti-angiogenic therapy (Escudier et al.).

3.5.1.3.7 miR-34a mimics MRX34

miR-34a inhibits osteoclastogenesis and bone resorption by targeting Tgif2. Its expression decreases during osteoclast differentiation. Nanoparticle-mediated delivery of miR-34a mimics alleviates bone metastasis in animal models of cancer. A Phase I clinical trial showed that lipid nanoparticle-encapsulated miR-34a (MRX34) has therapeutic potential for advanced/metastatic liver cancer and other malignancies (Beg et al.) .However, similar to odanacatib, there were immune-related adverse events, resulting in the premature termination of this clinical trial (NCT01829971).

3.5.1.3.8 BET inhibitors

At the epigenetic level of genomic regulation, members of the bromodomain and extraterminal (BET) family proteins—BRD2, BRD3, BRD4, and BRDT—play a crucial role as key regulators of gene expression. JQ1 selectively binds to BET bromodomain proteins, disrupting the activation of NFATC1 transcription by RANKL dependent on BRD4, thereby inhibiting osteoclast differentiation(Lamoureux et al.) .Moreover, in experimental models of osteoporosis and malignant osteolytic lesions, JQ1 was found to inhibit bone resorption (Baud'huin et al.) .Currently, JQ1 is in the preclinical development stage.

3.5.1.3.9 DOCK5 inhibitors

Dock5 regulates the small GTPase Rac, promoting the formation of sealing zones in osteoclasts. In vitro studies have shown that C21, as an inhibitor of Dock5, effectively prevents osteoclasts from absorbing bone. Furthermore, in an in vivo model of bone metastasis from osteosarcoma, C21 has been demonstrated to block bone destruction, currently in preclinical development(Vives et al.).

3.5.1.3.10 Jagged/Notch inhibitor

Jagged1, a pivotal molecule in the process of bone metastasis, meticulously activates the Notch signaling pathway within osteoclasts. This process acts as a "switch" that initiates osteoclast differentiation and functional enhancement, accelerating their maturation and differentiation while significantly promoting bone resorption and decomposition, thereby posing a threat to the stability and integrity of bone structures. Concurrently, the activation of Jagged1 indirectly influences the Notch signaling mechanism in osteoblasts, triggering a cascade reaction that leads to excessive production of IL-6 (Interleukin-6), an essential inflammatory factor that plays a complex yet crucial role in bone metabolism. The elevation of IL-6 levels further disrupts the normal balance of bone metabolism.

To address this challenge, scientists have conducted extensive research and successfully developed 15D11, a fully human monoclonal antibody. With its high specificity and affinity, this antibody precisely targets and inhibits the function of Jagged1, effectively blocking the bone metastasis process at its source. More importantly, the intervention of 15D11 significantly enhances the sensitivity of bone metastasis lesions to chemotherapy drugs, leading to a marked improvement in the efficacy of traditional chemotherapy treatments for these refractory tumors.

Additionally, it is noteworthy that another innovative drug, IVD11, is currently undergoing intense preclinical development. Although specific details have yet to be fully disclosed, based on its immense potential and promising prospects demonstrated during the research phase, IVD11 is expected to offer new therapeutic options and hope for patients suffering from bone metastasis in the future.

3.5.1.3.11 Proteasome inhibitors

Bortezomiba, the first proteasome inhibitor approved in the United States for the treatment of mantle cell lymphoma and multiple myeloma (Nakamura et al.) . Previous studies have demonstrated the anti-tumor effects of bortezomiba across various malignancies; however, clinical findings suggest limited efficacy of bortezomiba monotherapy in soft tissue sarcomas, thus recommending its use in combination with other drugs (Pasricha et al.) .In a spontaneous lung metastasis animal model, co-administration of erlotinib and bortezomiba effectively inhibits tumor growth and metastasis (Nakamura et al.) .Furthermore, in vitro experiments combining radium-223 with bortezomiba demonstrated synergistic effects, inhibiting proliferation of multiple myeloma cells (Suominen et al.).

3.5.2 By targeting osteoblasts to promote bone formation

3.5.2.1 Inhibitors of WNT signaling pathway

DKK-1 and SOST, as two crucial negative regulators, play a significant role in inhibiting bone formation in the human body. To overcome this physiological limitation, scientists have relentlessly worked and successfully developed specific inhibitors for DKK-1, namely BHQ880 and DKN-01. These innovative drugs are currently undergoing Phase I/II clinical trials for multiple myeloma and other solid tumors, aiming to evaluate their safety and preliminary efficacy.

Concurrently, another series of inhibitors targeting SOST, such as romosozumab, BPS804, and blosozumab, have progressed to more advanced Phase II/III clinical trials. Among them, romosozumab stands out particularly, as clinical studies have demonstrated that compared to placebos, this drug can significantly reduce the risk of vertebral fractures by up to 36% in postmenopausal women with osteoporosis, bringing hope to this patient population.

Furthermore, in laboratory research, anti-SOST antibodies have also shown immense potential. In animal models simulating multiple myeloma and breast cancer bone metastases, these antibodies significantly reduced the extent of osteolytic lesions, offering a novel approach to the treatment of cancer-related bone diseases. However, it is worth noting that while these research findings are encouraging, the specific efficacy and safety of anti-SOST

antibodies in real-world cancer patients still require further validation and confirmation through larger-scale and more rigorous clinical trials (Lamoureux et al.).

3.5.2.2 Endothelin-1 receptor inhibitors

Endothelin-1 has been found to play a significant role in the formation of osteoblastic lesions in preclinical studies. In Phase III clinical trials, the combination of endothelin-1 receptor antagonists with docetaxel did not improve the survival period of patients with metastatic castration-resistant prostate cancer, indicating that the clinical application of this combined treatment regimen may face challenges and limitations (Yin et al.; Carducci et al.).

3.5.2.3 Inhibitors of activin A

Activin A binds to ActRIIA/B receptors, activating ActRIB receptors, which triggers the phosphorylation of Smad2/3 to initiate signaling. ACE-011 (a fusion protein of ActRIIAc and human IgG Fc) promotes bone formation, inhibits bone resorption, and increases bone mass in non-human primates. The ActRIIA.muFc fusion protein promotes bone formation, slows bone destruction, and improves survival rates in mouse models of multiple myeloma. Clinically, sotatercept enhances bone formation and density in patients with multiple myeloma. These findings suggest that stimulating osteoblast-mediated bone formation may be an effective therapeutic strategy for promoting bone repair.

3.5.3 Targeting the bone matrix and microenvironment

3.5.3.1 Drugs targeting neural or osteogenic growth factors

During the progression of tumors, tumor cells, osteoclasts, and stromal cells collectively release a series of pain mediators, acting as "pain messengers" that acutely activate sensory nerve fibers within the bone, thereby triggering and intensifying patients' pain sensations. To tackle this challenge, the scientific community has conducted in-depth research and successfully initiated a Phase II clinical trial, focusing on evaluating the efficacy and safety of Tanezumab, an innovative drug, in patients with refractory bone metastases.

The trial results demonstrated that Tanezumab, as a potent inhibitor of nerve growth factor, exhibits a unique pharmacological mechanism of action. It precisely targets the TGF-β signaling pathway, modulating key components of this pathway to effectively suppress the transmission and amplification of pain signals, resulting in sustained relief of pain associated with refractory bone metastases. This discovery not only offers novel strategies and approaches for the treatment of bone metastasis pain but also provides patients with additional therapeutic options and hope (Sopata et al.).

Concurrently, with the deepening of research into the TGF-β signaling pathway, scientists have developed various novel TGF-β inhibitors. These inhibitors have demonstrated potent inhibitory effects on bone metastases in animal models, capable of disrupting the interactions between tumor cells and the bone microenvironment, thereby blocking the initiation and progression of bone metastases. This represents a groundbreaking advancement in the prevention and treatment of bone metastases (Fang et al.).

Table 1: Potential therapeutic targets and drugs under development for bone metastasis.

Medicine	Molecular target	Effect	Experimental ID/Developmental Status	Citation
Radium-223	NA（calcium-mimicking alpha-emitting isotope incorporated into bone）	The cytotoxicity of prostate cancer cells in areas of increased bone turnover and osteoblast activity in osteosclerotic lesions.	Clinical approval	(Parker et al.)
Abiraterone	Cytochrome P450 17α-hydroxylase	Improving the survival outcomes for patients with castration-resistant prostate cancer and delaying the time point of their first occurrence of skeletal-related events	Clinical approval	(Rizzo et al.; Iuliani et al.) (
Radium-223	NA（calcium-mimicking alpha-emitting isotope incorporated into bone）	The toxicity of prostate cancer cells is enhanced in the bone sclerosis region, where bone turnover is accelerated and osteoblast activity is increased.	Clinical approval	(Harbeck and Gnant)
Enzalutamide	Androgen receptor	Optimize the treatment and prognosis for patients with castration-resistant prostate cancer.	Clinical approval	(R. E. Coleman, M. Collinson, et al.)
Bisphosphonates	Phosphofructokinase	Inhibition of osteoclast activity and tumor cell homing to bone	Clinical approval	(Stopeck et al.; Walsh)
Denosumab	RANKL	Inhibit bone resorption by suppressing osteoclast differentiation and activity	Clinical approval	(Nakai et al.)
AS2676293	LGR4-ECD	Inhibit osteoclast differentiation and osteolytic lesions induced by breast cancer.	During experimentation	(Liang et al.; Jensen et al.)
Odanacatib	Tissue protease K	Prevent the progression of osteolytic lesions in the body and reduce the clinical manifestations of bone resorption.	NCT00399802	(Irelli et al.; Hurvitz et al.)
Everolimus	Mammalian targets of rapamycin	Inhibit bone resorption and block osteoclast differentiation	Clinical approval	(Koreckij et al.; Yu et al.)
Dasatinib、	Cyclin-dependent kinase and proto-	Inhibit bone turnover markers in prostate cancer patients	NCT00410813	(Sousa and Clézardin)

saracatinib、bosutinib	oncogene tyrosine kinase		NCT00918385	
BMS777607、ASLAN002	Tyrosine kinase receptors expressed by osteoclasts	Animal models have demonstrated the inhibition of osteolytic lesion formation, which in turn leads to a decrease in bone resorption among advanced cancer patients.	NCT01721148 NCT00605618	(D. C. Smith et al.; M. Smith et al.; Escudier et al.)
Cabozantinib	Vascular endothelial growth factor receptor 2, a cell surface receptor	Reduce tumor burden and diminish osteoblastic disease	Clinical approval	(Beg et al.)
miR-34a	Osteoclastogenic factors	Targeting pre-osteoclast factors to reduce bone metastasis	NCT01829971	(Sousa and Clézardin)
JQ1	Bromodomain and extra-terminal domain (BET) family proteins	Inhibit osteoclast formation and bone destruction in osteosarcoma experimental models	Preclinical	(Sousa and Clézardin)
C21	dedicator of cytokinesis 5	Reduce in vitro osteoclast activity and bone destruction in a mouse model of melanoma	Preclinical	(Sousa and Clézardin)
IVD11	Jagged or Notch	Inhibit in vivo osteoclast formation and bone metastasis formation	Preclinical	(Oyajobi et al.)
Bortezomiba	26S proteasome	Stimulate bone formation in patients with multiple myeloma, promoting bone healing	NCT01286077 NCT00972959	(Iyer et al.)
BHQ880、DKN01	Dickkopf-1	Suppression of osteolytic lesions in mouse models may contribute to increased bone density in patients with relapsed or refractory multiple myeloma.	NCT01302886 NCT01337752 NCT00741377	(Cosman et al.; McDonald et al.)
blosozumab, BPS804、romosozumab	Scleroprotein	Bone resorption is reduced in cancer or multiple myeloma mouse models.	NCT01575834	(Yin et al.; Carducci et al.)

Atrasentanb、zibotentan	Endothelin-1	Failed to achieve improvement in the primary endpoint in Phase III trial	SWOGS0421	(McDonald et al.; Chantry et al.)
Sotatercept	Protein kinase A	Improvement of bone density	NCT01562405 NCT00747123	(Aiello et al.)

3.6 The potential of bone turnover markers

Even when bone metastasis has occurred, it remains asymptomatic in many sites, presenting with highly diverse clinical manifestations (Clézardin et al.) .In the intricate process of tumor metastasis, the delicately regulated balance between osteoclasts and osteoblasts is disrupted, leading to a series of biochemical reactions within the bone microenvironment. This imbalance triggers the release of specific bone-derived molecules into the bloodstream. Acting as "messengers" of bone metastasis, these molecules can be captured and measured through advanced non-invasive detection techniques, providing invaluable diagnostic information for clinicians (as demonstrated in studies by McCaffrey et al.). Currently, the medical community widely acknowledges a series of biochemical markers as crucial indicators for assessing bone formation and resorption activities. Among them, bone-specific alkaline phosphatase (BSAP) stands out as an important marker for evaluating bone formation due to its high specificity to osteoblast activity. Additionally, type I collagen, the primary component of bone matrix, releases its carboxy-terminal and amino-terminal propeptide fragments early during bone formation, making them sensitive indicators of bone formation as well. However, their routine use is constrained by high individual variability (D'Oronzo, Brown and Coleman).

4. SUMMARIZE

Bone metastasis is extremely common and can be devastating for patients, particularly in cases of breast cancer, prostate cancer, and lung cancer, which are prone to metastasize to bone. Bone metastases lead to the formation of secondary tumors, causing a range of complications or recurring years later, significantly affecting the morbidity and mortality rates of patients with advanced cancer. This paper provides a detailed overview of the current clinical diagnostic methods along with their respective advantages and disadvantages. By building on existing research, we can anticipate future developments; several new targeted therapies have already entered clinical development, aiming to effectively block the progression of skeletal lesions through various mechanisms. We hope that by gaining a deeper understanding of the basic biology, biomechanics, and molecular mechanisms of bone metastasis, we can continuously identify new and effective therapeutic targets to prevent bone metastasis and improve survival rates for patients with bone metastases.

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