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Palliative Management of Metastatic Bone Disease

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ABSTRACT

Metastatic Bone Disease (MBD) is the most common primary malignant bone tumor, predominantly affecting adolescents and young adults. Advances in therapeutic strategies, including neoadjuvant chemotherapy, surgery, and limb reconstruction, have significantly improved the 5-year survival rate for non-metastatic cases to 60–70%, compared to historical rates of only 10–20%. Key prognostic factors include histological response to preoperative chemotherapy, alkaline phosphatase levels, and lactate dehydrogenase. However, prognosis remains poor for patients with metastases, particularly pulmonary metastases, or tumors located in the pelvis and axial skeleton. Data from Indonesia reveal relatively low survival rates, with a mean survival of only 28 months, indicating limited access to optimal treatment. Recent research developments, such as gene therapy, immunotherapy, and advanced reconstructive techniques, hold promises for improving therapeutic outcomes and patient quality of life in the future.

Keywords: MBD, neoadjuvant chemotherapy, prognosis, limb reconstruction, gene therapy.

INTRODUCTION

Metastatic Bone Disease (MBD) is a clinical condition involving the spread of malignant cancer cells from a primary site to bone tissue. This metastatic process makes bone one of the organs that often become the main target after the lungs and liver. When cancer cells spread and settle in the bone, this can lead to structural and functional damage, which can complicate treatment efforts and worsen the patient's prognosis. Lung and prostate cancer have a dominant involvement, accounting for up to 70% of MBD cases. The importance of understanding MBD lies in its impact on patients, including the level of difficulty in pain management, maintenance of bone function, and maintenance of overall quality of life. In this context, in-depth research and understanding of the factors that influence the onset, progression, and management of MBD are essential. Based on World Health Organization (WHO) data, it shows that the total number of cancer cases in Indonesia in 2020 reached 358,809, with breast, cervical, and lung cancer as the main causes of mortality. Patients diagnosed with cancer require long-term care, and pain and symptom control are priorities in cancer control programs. However, a major challenge arises when patients reach advanced, untreatable stages of the disease, so palliative care for pain and symptom control becomes the main focus in cancer management.

Palliative Care for MBD is the main focus in efforts to provide holistic care for patients facing the clinical complexities and serious impacts of the spread of cancer cells to bone tissue. Therefore, palliative care plays a very

important role in managing symptoms and improving the quality of life of patients facing MBD. Palliative care aims to provide comprehensive support, not only in overcoming physical pain, but also paying attention to psychosocial, spiritual, and overall well-being of the patient. A deep understanding of the unique challenges faced by patients and their families is very important in designing and formulating effective treatment strategies. It is important to further explore innovative and holistic palliative care strategies that can provide maximum benefits for MBD patients. Research and development of health policies focusing on palliative care can help create practical guidelines to guide professionals' health in providing sensitive care appropriate to the needs of patients and their families. A comprehensive understanding of the palliative management of the metastatic process is important in finding therapeutic steps for complete treatment. In this review, the author explores the latest advances in the field of metastasis and highlights the latest insights that contribute to palliative care in patients with MBD.

METHODS

Study Design

This study is designed as a narrative literature review aimed at summarizing current knowledge and recent advancements in the understanding and palliative management of Metastatic Bone Disease (MBD). The review focuses on comprehensively understanding MBD, including its definition, epidemiology, diagnosis, and the various non-operative and operative palliative treatment modalities, with the ultimate goal of improving pain management, enhancing functional independence, preventing tumor progression, and improving the overall quality of life for patients and their families.

Search Strategy

A comprehensive literature search was conducted using electronic databases, including, but not limited to, PubMed, ScienceDirect, Scopus, and Google Scholar, covering publications from approximately 2000 to the present. This timeframe is chosen to capture recent advancements and current perspectives on MBD and its management, aligning with the review's goal of exploring latest advancements. Search terms included: "Metastatic Bone Disease," "MBD," "Palliative care," "Analgesics MBD," "Radiotherapy MBD," "Bisphosphonates MBD," "Denosumab MBD," "Electrochemotherapy MBD," "Embolization MBD," "High-Intensity Focused Ultrasound MBD," "Operative management MBD," "Diagnosis MBD," and "Prognosis MBD." Boolean operators (AND/OR) were used to refine search queries (e.g., "Metastatic Bone Disease AND palliative management," "MBD AND diagnosis," "palliative care AND bone metastasis").

Eligibility Criteria

The review included:

- Peer-reviewed original articles, systematic reviews, meta-analyses, and clinical guidelines relevant to Metastatic Bone Disease and its palliative management, as evidenced by the extensive citations of various research papers and guidelines within the source.
- Studies published in English or Indonesian, reflecting the language of the provided source and its cited materials.
- Research involving human subjects, focusing on clinical aspects, diagnosis, treatment modalities, and prognosis of MBD.
- Studies were excluded if they were case reports with insufficient data, preclinical studies with animal models only, or non-peer-reviewed sources such as conference abstracts or editorials, to maintain the rigor and clinical relevance of the review.

Data Extraction and Analysis

Relevant data were extracted and organized into thematic categories, including epidemiology, clinical presentation,

imaging, histopathology, treatment strategies (chemotherapy, surgical options, and reconstruction techniques), and survival outcomes. Key findings were synthesized and compared across studies to highlight consensus, differences, and emerging trends. No statistical meta-analysis was performed, as the aim of this review was qualitative synthesis.

Quality Assessment

The quality of included studies was assessed using adapted checklists from the Joanna Briggs Institute (JBI) and the PRISMA guidelines for literature reviews. Only studies with moderate to high methodological quality were included in the final synthesis.

RESULTS AND DISCUSSION

Definition of MBD

Metastasis is defined as the transmission of pathogenic microorganisms or cancer cells from an initial location to one or more other locations in the body, usually through blood vessels or lymph. MBD is a clinical condition characterized by the spread of malignant cancer cells from a primary site to bone tissue. This process involves complex stages where cancer cells detach from the primary tumor, invade blood or lymphatic vessels, and spread to bone, creating lesions that can affect bone structure and function. MBD is one of the malignant types often found in bone, with an estimated 20% of all cancer patients experiencing bone metastasis with complaints. Post-mortem examination shows bone metastasis in 70% of cancer patients.

Epidemiology of MBD

Bone is the most common site for secondary metastasis, especially after metastasis in the lungs and liver. Bone metastasis is a malignant tumor from an extraosseous organ or tissue. These metastatic cells are transferred through the lymphatic vascular system to the bone, where they then continue to grow and form a tumor. According to the American Cancer Society, approximately 400,000 new cases of malignant bone metastasis are diagnosed in the United States annually. The incidence of advanced malignant tumors with bone metastasis is 30–75%, especially common in patients with advanced prostate cancer and breast cancer.[15] Metastasis often occurs in breast cancer (65–75%), prostate cancer (65–90%), and lung cancer (17–64%), and less frequently in thyroid cancer (65%), bladder cancer (40%), melanoma (14–45%), kidney cancer (20–25%), and colon cancer (10%). Bone lesions are found in 70–95% of cases of multiple myeloma.

With the extension of patient life expectancy due to cancer treatment, the number of patients with bone metastasis is estimated to continue increasing. Bone metastasis can cause various complications, including pain, pathological fractures, compression of the spinal cord or nerve roots, and life-threatening hypercalcemia[22]. The most common regions for bone metastasis include the spine, pelvis, ribs, skull, proximal humerus, and femur. Bone lesions metastatic can alter the structural integrity of bone, leading to an increased risk of skeletal related events (SRE) such as pathological fractures, spinal cord compression, hypercalcemia, and severe bone pain requiring radiotherapy, surgery, or palliative management. The MBD process produces radiolucent (lytic) lesions that have a higher fracture rate than cancers that produce radiodense (sclerotic) lesions.[8]

Types of MBD

Bone metastases are classified as osteolytic, osteoblastic, or mixed, according to the main mechanism of interference with normal bone remodeling:

Osteolytic Lesions

Characterized by normal bone destruction, often found in multiple myeloma (MM), renal cell carcinoma, melanoma, non-small cell lung carcinoma, non-Hodgkin lymphoma, thyroid cancer, or Langerhans cell histiocytosis. Most breast cancers result in osteolytic bone metastases. Bone destruction is primarily mediated by

osteoclasts and is not a direct effect of tumor cells. Other mechanisms include vascular compression and resulting ischemia in late-stage cancer. Parathyroid hormone-related peptide (PTHrP) plays a major role in the development of osteolytic lesions. It is not clearly understood whether the bone microenvironment induces cancer cells to express PTHrP or if cells metastasizing to bone have inherently higher PTHrP expression. Receptor activator of NF-kappaB ligand (RANKL) plays an important role in osteoclast formation by stimulating precursor cells when binding to receptor activator of NF-kappaB (RANK) on the osteoclast precursor cell membrane.[18]

Osteoblastic Lesions

Characterized by new bone deposition, often found in prostate cancer, carcinoid, small cell lung carcinoma, Hodgkin lymphoma, or medulloblastoma. The mechanism of osteoblastic metastasis is less understood. In some cases, new bone formation does not necessarily have to be preceded by bone resorption. Transforming growth factor, bone morphogenic protein (BMP), and endothelin-1 are associated with osteoblast formation. Prostate-specific antigen (PSA) can cleave PTHrP, allowing osteoblastic reactions to dominate by decreasing bone resorption processes. In addition, core binding factor alpha1 (Cbfa1) or also known as Runx-2 will affect the osteoblast differentiation process.[18]

Mixed Lesions

If the patient has both osteolytic and osteoblastic bone lesions as found in breast cancer, gastrointestinal cancer, and squamous cancer. Although breast cancer primarily originates from osteolytic lesions, 15-20% of women with breast cancer will have osteoblastic lesions, or both types of lesions.[18]

Diagnosis of MBD

A thorough patient health history should be taken to identify a history of malignant tumors, both personal and family, cancer risk factors, and systemic symptoms. Physical examination is important to identify the exact area of pain and the presence or absence of a soft tissue mass. If the tumor originates from bone, the soft tissue mass should not move over the bone. Neurovascular disorders and distal edema are rare in bone metastasis[4,13]. Laboratory examinations can provide some clues that can facilitate the determination of the lesion's degree. The most important laboratory examinations in the evaluation of adults with bone lesions are serum calcium, serum immunoglobulin, prostate-specific antigen, and erythrocyte sedimentation rate measurements.

Hypercalcemia is not uncommon in patients with multiple myeloma or metastatic cancer, and can be life-threatening. Serum protein electrophoresis with a monoclonal protein spike is indicative of myeloma. Increased serum prostate-specific antigen levels are characteristic of prostate carcinoma. Erythrocyte sedimentation rate is a nonspecific examination that is often increased in individuals with infections, immunological disorders, or marrow cell neoplasms such as lymphoma, Ewing sarcoma, histiocytosis, or leukemia. Pregnancy tests are mandatory for women of childbearing age for safety in further radiographic imaging.[4]

Radiography is the primary imaging modality and can help diagnose MBD by providing information about the location, bone response (lytic or sclerotic), size, and number of lesions, as well as the possibility of pathological fractures and/or soft tissue involvement. In a large number of cases, additional imaging is required. Bone lesions in patients with known primary malignancy should be considered bone metastases unless there are atypical features. Often, MBD itself is not visible on radiographs unless the tumor is mineralized or leads to clear osteolysis, such as in focal myeloma lesions, which are visible when more than 50% of the bone substance has disappeared. Therefore, tumor detection and diagnosis depend on the tumor's effect on the bone.[17] The extent of bone damage caused by MBD lesions rather

than the tumor itself is what is often depicted on radiographs. For purely medullary tumors, at least 50% damage to the trabecular bone architecture must exist before the tumor can be seen on radiographs.

Small lesions are easily missed on radiographs, especially in patients with low bone mineral density (osteoporosis). Trabecular bone density is higher in the epiphysis and metaphysis compared to the diaphysis, making tumors in the epiphysis and metaphysis easier to detect than in the diaphyseal medulla, due to better lesion contrast against adjacent normal trabeculae. Similarly, the diagnosis of bone tumors on radiographs is also delayed when lesions are located in flat bones, axial skeleton, and ribs, because changes in bone appearance are difficult to see with superimposition of anatomical structures in the surrounding area[13]. Pedicle involvement, which is one of the typical features of bone metastasis, is very well seen in the anteroposterior position which will show the appearance of a missing 'eye' of the vertebra. The appearance of these metastatic lesions also affects the interpretation of plain bone X-rays. Permeative lesions are difficult to detect until extensive medullary involvement occurs.

Purely lytic metastatic lesions are also difficult to see until extensive involvement occurs unless there is cortical involvement. In lesions with a mixed lytic/blastic appearance, the surrounding sclerotic area resembles a normal bone reaction in its attempt to wall off the metastasis. Pure blastic lesions are easier to see, where the sclerotic area shows ill-defined borders caused by a reaction to osteoblast growth factors produced by surrounding normal bone cells to isolate the abnormal focus. Due to the lack of sensitivity of plain X-rays to assess bone metastasis, plain X-rays are often combined with other imaging modalities[16,20].

Bone scintigraphy using Tc-99m phosphate is the preferred method as a screening tool to assess bone metastasis in both symptomatic and asymptomatic patients. This examination has high sensitivity but low specificity, so positive findings must be confirmed with physical examination or other supporting examinations. Bone scintigraphy is an indicator of osteoblastic activity. The radioactive diphosphonate complex is absorbed by the bone surface and enters hydroxyapatite crystals, especially in areas where new bone formation or increased osteoblast activity occurs. This process will appear as an area that is more enhanced due to high uptake. There are two factors that influence phosphonate accumulation in bone, namely blood flow and the efficiency of phosphonate extraction[10,21]. In purely osteoblastic lesions, such as in prostate cancer, the bone scan results will show very high uptake in the metastatic area. Osteolytic lesions in most cancers will still appear as areas with increased uptake, this is because in the normal bone area around the osteolytic lesion there is still bone formation as a compensatory mechanism. Only in some conditions, such as multiple myeloma, bone scan results show normal images or cold spots due to purely osteolytic lesions.

This can also occur in very aggressive osteolytic lesions where the tissue around the tumor is unable to compensate[20]. Increased uptake can also be seen in lesions where there is increased osteoblastic activity such as fractures, infections, inflammation, post-surgery, and degenerative processes. Correlation with plain X-rays is necessary in situations that may cause doubt. Increased activity in multiple areas of varying size with the main lesion located in the axial area, is very suggestive of metastasis. Of the metastatic lesions seen on bone scans, 39% are seen in the vertebrae, 38% in the ribs and sternum, 12% in the pelvis, and only 10% in the skull and long bones. It is estimated that only 50% of single lesions on bone scans are metastasis[10,13]. CT-Scan has better sensitivity compared to plain X-rays and can better localize lesions in the bone. However, due to higher cost and longer procedure time, CT-Scan is not used as a screening tool for bone metastasis. CT-Scan is more often used to see the extent of cortical bone damage and to assess the risk of pathological fractures, and it is also useful as a supporting tool for

biopsy if needed[10,13]. One of the main assessments in CT-Scan for diagnosing metastasis is cortical involvement. For most types of cancer, CT is the imaging modality of choice for staging in the chest and abdomen and for serial imaging follow-up. CT scans for this purpose cover most of the axial skeleton and thus can detect not only soft tissue lesions but also osteoplastic or osteolytic bone metastases. CT is also used to assess the stability of bone structures harboring metastasis, especially in complex anatomical areas, and to obtain better structural definition of abnormal findings seen on scintigraphy or MRI. CT is the imaging method of choice in situations because it allows visualization of both trabecular and cortical bone with high resolution. MRI is excellent for assessing bone marrow involvement. Due to its excellent soft tissue resolution, MRI is the best imaging modality option for assessing metastasis spread in the bone marrow cavity, as well as tumor extension from the bone marrow cavity and involvement of surrounding structures. Indications for MRI use for bone metastasis are to differentiate bone compression due to benign or malignant lesions, clarification of inconclusive findings on bone scans and radiographs, detection of early-stage metastasis, evaluation of tumor expansion into surrounding tissues, and assessment of therapeutic response.[13,23]

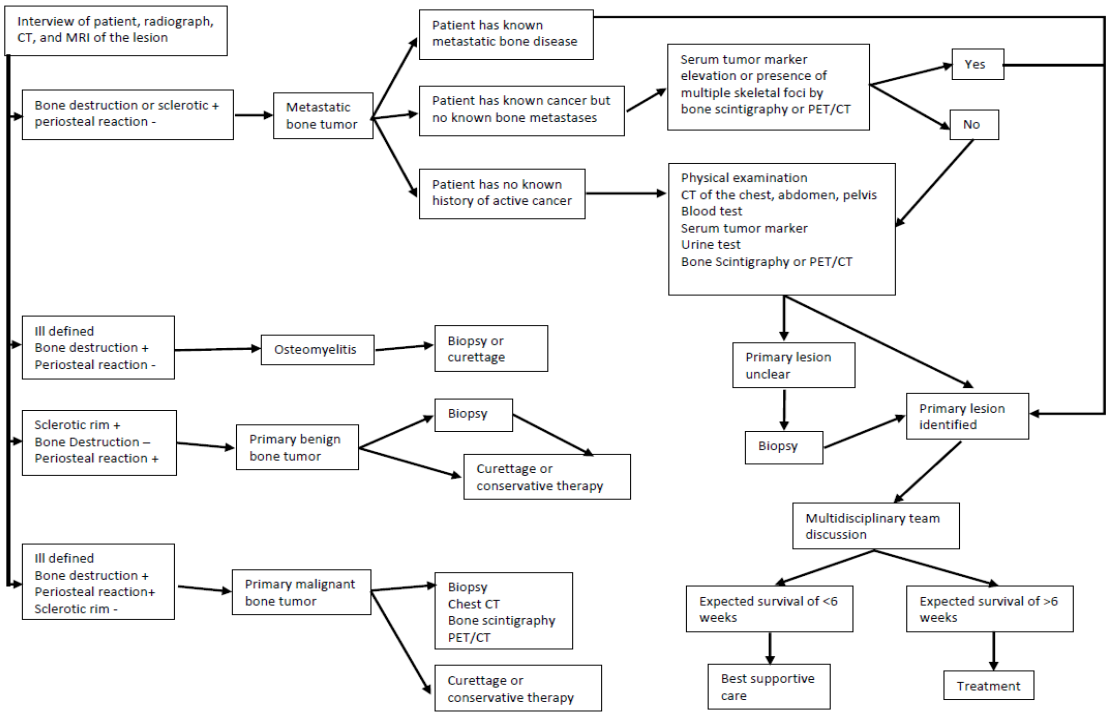

Figure 1. Diagnosis Algorithm of MBD[22]

Palliative Management of MBD

Analgesics

Analgesics, including NSAIDs and opioids, are the first line of pain management in patients with symptomatic bone metastasis. NSAIDs have long been used to control pain for various diseases. NSAIDs also have anti-inflammatory effects that make them ideal drugs for inflammation caused by certain types of cancer during extensive tissue invasion and destruction. The basic mechanism of these drugs is to inhibit the cyclooxygenase (COX) enzyme involved in prostaglandin production, which regulates various cell functions including pain perception. In tumor cells, COX-2 activity is increased. Therefore, reducing COX activity will also inhibit pain perception. To support this idea, acute administration of COX-2 selective inhibitors in mice with cancer-induced bone pain was performed and the experiments showed reduced (pain)

behavior, while chronic administration also reduced osteoclast destruction in addition to significant pain relief. The main weakness is its limited effect due to its short duration of action and lack of long-term effect. The second most commonly used drug is opioids. Opioids are one of the most effective and widely used drugs for cancer pain, producing long-lasting analgesic effects. The analgesic effect of opioids largely depends on μ receptor saturation and is thus influenced by the type and severity of pain, previous opioid exposure, and receptor distribution. The main side effects of opioid drugs are physiological dependence, tolerance, addiction, sedation, constipation, nausea, vomiting, and respiratory depression, which limit their further use[2].

Bisphosphonates are drugs commonly used to treat hypercalcemic conditions in the body. These drugs increase the acidity of the local bone tumor microenvironment, causing a decrease in bone destruction and thus reducing the activation of acid ions and reducing pain due to cancer. These drugs are safe to use but have not been proven to be the most effective treatment model for pain relief due to cancer metastasis.[2,5] Endothelin-1 (ET-1) is a neurotransmitter secreted by neuronal cells, non-neuronal cells, and tumor cells. Hyperalgesia in bone metastasis occurs due to sensitization of primary afferent nociceptors containing ET-1 receptors. Therefore, ET-1 receptor antagonists can reduce bone pain by counteracting the stimulatory effects on nociceptive receptors. These antagonists also have an indirect effect in reducing cellular junction disruption and preventing metastasis.[2,9] Radiotherapy is the preferred modality for treating localized pain in bones caused by metastasis. As many as 70-80% of patients experience a response to radiation and about one-third experience a complete response[1]. Radiotherapy relieves pain in 75-90% of cases, thereby reducing the need for pain medication and reducing its side effects. This leads to an improvement in quality of life (QOL). Since it takes several weeks to achieve maximum effect, patients still require pain medication while waiting for the effect to appear.[3]

Radiotherapy

Radiation therapy can be given using three forms of treatment: local field radiation therapy, wide field radiation therapy, and radionuclide therapy. Local field radiation therapy is considered a conventional treatment for bone metastasis. It treats the involved bone and produces a pain relief rate of 80-90%. Several randomized trials have shown that a single fraction of 8Gy is sufficient to relieve pain. Wide-field radiation (half-body, hemibody). This therapy can be used as primary palliative therapy for widespread symptomatic bone metastasis or as an adjunct to local field radiation to reduce the expression of hidden metastases later and to reduce the frequency of re-treatment. It is possible to differentiate: upper wide field treatment (from skull or C1 to L2-3) - the optimal single dose is 6Gy; mid-body wide field treatment (from L1 to the upper third of the femur) - the optimal single dose is 8Gy; lower wide field treatment (from L3-4 to above the knee) - the optimal single dose is 8Gy.

Wide field radiation provides pain relief for 64-100% of patients and approximately 50-66% of patients maintain pain relief for the rest of their lives. The radiation field should be shaped to reduce exposure to sensitive structures such as the lungs, intestines, kidneys, and liver. Radionuclide therapy is the systemic use of radioisotopes for bone pain. Radiopharmaceuticals such as strontium-89, rhenium-186, or samarium-153, have proven effective in the palliation of metastatic bone pain. They are preferentially taken up at sites of bone formation, thus perhaps being most effective for osteoblastic metastases. Their main side effects are myelosuppression and rebound pain. Postoperative radiotherapy after surgical stabilization has been associated with a decrease in secondary surgical procedure rates and an improvement in functional status. Radiotherapy improves remineralization and bone healing and

prevents loss of surgical fixation by treating residual tumor. A retrospective review of 60 patients with weight-bearing bone metastatic disease with pathological fractures or impending pathological fractures showed that surgery followed by radiotherapy was associated with improved functional status and overall survival. For patients who do not require surgery, consulting radiation oncologists should consider factors such as the location of metastasis in weight-bearing and non-weight-bearing bones, the size and extent of metastasis, and related symptoms when making treatment recommendations.
In patients at risk of bone fracture due to bone metastasis, bisphosphonates should also be considered as part of the treatment regimen.[11]

Biphosphonates and Denosumab

The primary tumor histology is the most important factor in selecting chemotherapy regimens aimed at controlling tumor progression and preventing the development of bone-related events. Bisphosphonates indirectly reduce osteoclast activity by affecting osteoblasts, and directly induce osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase. Among intravenous agents, zoledronic acid is approved for the treatment of bone metastases in solid tumors and multiple myeloma, and pamidronate is approved for patients with breast cancer and multiple myeloma. Ibandronate can be given intravenously and orally and is effective for bone metastases in breast cancer patients. Oral clodronate is another treatment option for osteolytic bone metastasis. For breast cancer, bisphosphonates should be given as soon as bone metastasis appears, even if asymptomatic. In prostate cancer, patients with hormone-sensitive disease have a lower risk of developing bone-related events, so bisphosphonates should only be given to castration-resistant patients. Bisphosphonates should be considered in patients with bone metastasis from other malignancies who experience symptomatic bone-related events. Zoledronic acid is most effective in reducing serum calcium levels in patients with hypercalcemia, a serious and potentially life-threatening complication of osteolytic bone metastasis. Bisphosphonates have a risk of side effects such as osteonecrosis of the jaw, renal failure, and hypocalcemia. Zoledronic acid is usually given every 3-4 weeks. However, less intensive schedules (every 12 weeks) were reported to be no less important in breast cancer, prostate cancer, and multiple myeloma. Therefore, a three-month schedule can reduce the risk of side effects without affecting treatment outcomes[22].

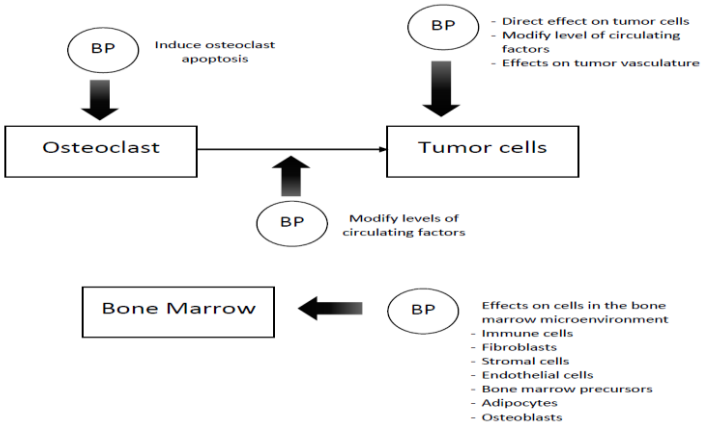

Figure 2. Biphosphonates role in MBD[22]

Denosumab is a human monoclonal antibody that targets receptor activator of NF-κB ligand (RANKL), a protein that acts as a key signal to promote bone loss, inhibiting the interaction between RANKL and RANK and, therefore, reducing osteoclast maturation and activity. Denosumab guidelines for metastatic bone disease are similar to bisphosphonate guidelines. However, denosumab is not nephrotoxic and

can be used in patients with renal failure. Hypocalcemia and osteonecrosis of the jaw are the most common complications of denosumab. Currently, there is no evidence to support reducing the frequency of denosumab treatment; unlike bisphosphonates, denosumab does not accumulate in bone, even after months, and its discontinuation can compromise therapeutic effects.

Lipton et al. conducted a randomized controlled trial comparing denosumab and zoledronic acid for their ability to prevent bone-related metastatic events in various types of cancer. Denosumab was superior to zoledronic acid in preventing bone-related events in patients with bone metastasis, regardless of Eastern Cooperative Oncology Group performance status, presence/absence of initial visceral metastasis, number of bone metastases, and urinary N-telopeptide levels. Chen et al. conducted a meta-analysis of six randomized controlled trials to compare the safety of denosumab and zoledronic acid for bone metastasis.[24]

Regarding mild side effects, anemia and anorexia were more common in the zoledronic acid group, but the incidence of back pain, nausea, fatigue, constipation, bone pain, arthralgia, and vomiting did not differ between the two groups. Regarding serious side effects, there was no difference in osteonecrosis of the jaw between the two groups; however, renal side effects were more common in the zoledronic acid group, and hypocalcemia and new primary malignancies were more common in the denosumab group.[22]

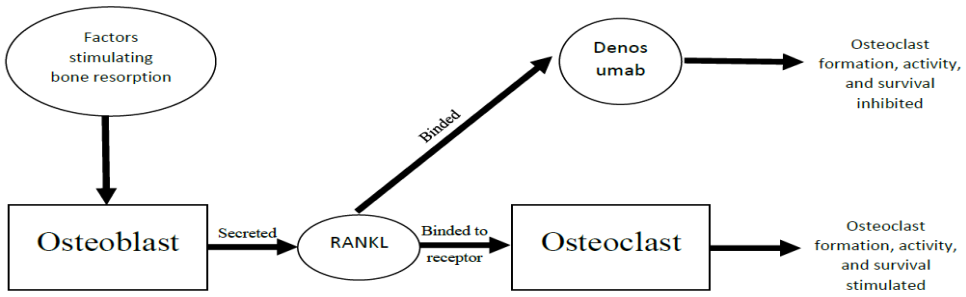

Figure 3. Denosumab mechanism of actions in limiting osteoclast activity

Electrochemotherapy

Electrochemotherapy consists of a combination of electricity and intravenous chemotherapy drug infusion. Cell membranes are usually poorly or non-permeable, but electrical impulses induce the opening of transmembrane channels, allowing chemotherapeutic agents to enter cells and enhancing local cytotoxic effects. Bleomycin and cisplatin have proven to be the most effective and appropriate electrochemotherapy agents for clinical use. Recently, electrochemotherapy has become available for bone metastasis, improving pain relief and local control of bone metastasis in patients who failed radiotherapy or who had difficulty undergoing surgery. The mineral structure of bone is not changed by electrochemotherapy, and nerve structures show temporary edema without structural changes after electroporation. This is the main advantage of electrochemotherapy compared to radiotherapy and other ablation techniques. Cornelis et al reported that electrochemotherapy was performed on two patients with spinal metastasis and spinal cord compression to relieve pain, improve motor function, and control tumor growth without complications, such as exacerbation of paralysis. Campanacci et al. conducted a prospective multicenter study of 102 patients with bone metastases who underwent electrochemotherapy. Twenty-four patients (24%) received an intramedullary nail scheduled after electrochemotherapy in the same surgery. Treatment response according to Response Evaluation Criteria in Solid Tumors was 40% objective response, 51% stable disease, and 9% progressive disease.

Breast cancer diagnosis and performance status 0 to 1 were significantly associated with objective response. During follow-up, a significant decrease in pain and a significant improvement in quality of life were observed.[22]

Embolization

Embolization is a useful adjunctive procedure for the treatment of metastatic bone disease. Since all metastatic bone lesions are hypervascular, all patients may be indicated for embolization. Indications for bone metastasis embolization are palliative including hemorrhage control, facilitation of subsequent surgery, inhibition of tumor growth, and pain relief due to decreased tumor volume and pressure on the richly innervated periosteum and surrounding structures. Indications for repeat embolization are pain and/or imaging evidence of progressive disease. Preoperative or serial embolization techniques using gelfoam, PVA particles, alcohol emulsion, coils, tissue adhesives, ethanol, and microfibrillar collagen can be used as primary or adjunct treatment for surgery or radiation therapy. Serial embolization aims for devascularization, size reduction, marginal calcification, and pain relief. It is usually performed at 4 to 6-week intervals until symptomatic improvement or disappearance of tumor vascularity as assessed by angiography, magnetic resonance imaging, or computed tomography scans. Preoperative embolization provides tumor devascularization; typically, surgery should be performed within 24-48 hours after embolization to prevent recanalization. Embolization can also be used to palliate bone pain and prevent further tumor growth in patients who are not candidates for surgery. With hyperselective catheterization and embolization of pathological feeding arteries to the lesion with the most appropriate embolic agent, embolization is expected to be successful in 90% of cases; several procedures are often required.[19]

High-Intensity Focused Ultrasound (HIFU)

HIFU causes coagulative necrosis at a thermal threshold of 65°C to 85°C, depending on the tissue absorption coefficient. High-intensity focused ultrasound beams result in precise localization within a small volume, minimizing potential thermal damage to tissues outside the focal region. MRI-guided focused ultrasound surgery (MRgFUS) combines high-intensity focused ultrasound with MRI guidance, and has been approved for pain relief in patients with bone metastasis by the US FDA. In one study, MRgFUS relieved pain in 60-100% of patients; pain relief occurred quickly and lasted for more than 3 months. MRgFUS is recommended as a second-line treatment for pain relief in non-vertebral and non-skull metastasis after radiotherapy failure. There are no limitations based on bone lesion type (osteolytic or osteoblastic) or number of bone lesions. Treatable lesions should always be identifiable on images and limited to non-articular areas on the extremities, ribs, sternum, pelvis, shoulder, lumbar spine, and posterior sacrum. Further inclusion criteria are that the lesion must be at least 10 mm below the skin surface, and the ultrasound beam path must always reach the target lesion without encountering other structures with high absorption or reflection properties (such as non-target bone, air-filled organs, wide scars, or metal implants/devices), as these protect against ultrasound scattering and obscure targets beyond them.

Tsai et al. investigated factors correlated with treatment efficacy in 31 patients with bone metastasis treated with MRgFUS. The overall clinical response rate was 84%, and the radiographic response rate was 68%. Multivariate analysis showed that good Karnofsky performance status and large lesion coverage volume (thermal ablative tumor volume/pre-treatment tumor volume × 100%) correlated with higher therapeutic effect. According to the literature, the clinical response rate after MRgFUS ranges from 64% to 76%. In one randomized controlled

study, the MRgFUS group showed a better response rate compared to the placebo group (64% vs 20%, p <0.001). The most common complication during MRgFUS treatment was pain (32%). Third-degree skin burns or fractures also occurred in 3% of patients \. In addition, a paired-design study compared MRgFUS and conventional radiotherapy in terms of efficacy as a first-line local treatment, and MRgFUS had a higher response rate 1 week after treatment (71% vs. 26%, p = 0.0009). A randomized controlled trial from the Dutch Bone Metastasis Study database showed that MRgFUS was more effective when Karnofsky performance status was good and breast or prostate cancer was the primary cancer type. Treatment of spinal bone metastasis is currently not performed in clinical practice due to concerns about heat damage to the spinal cord.[22]

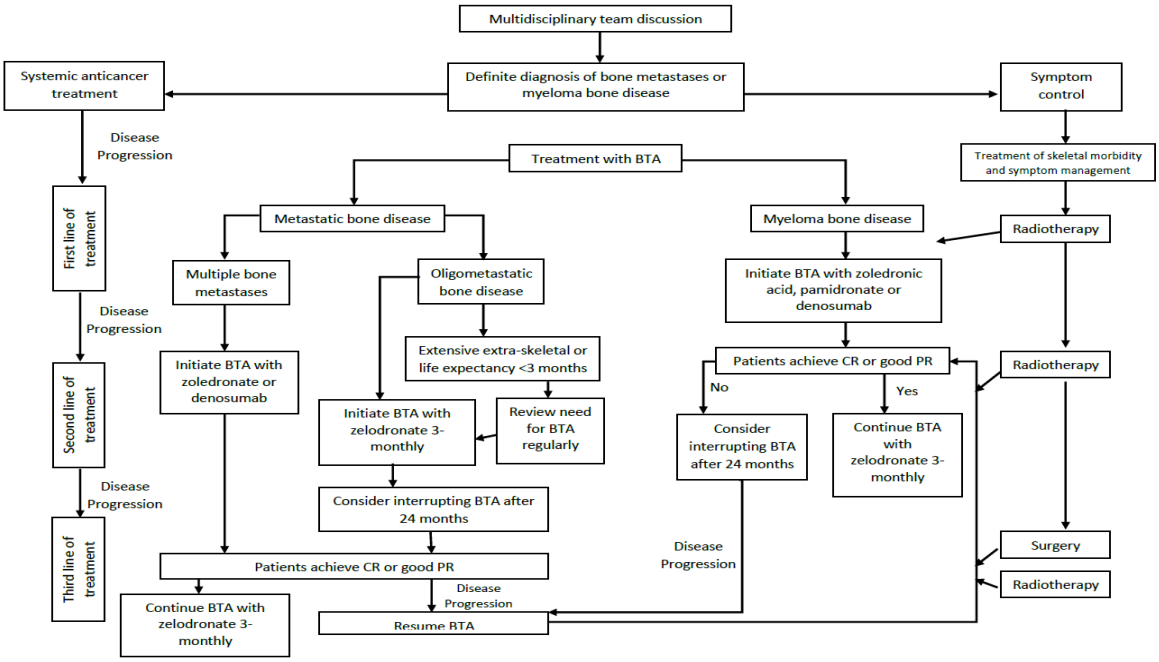

Figure 4. Multidisciplinary Management Algorithm for MBD.[7]

Operative

Indications for surgical intervention for bone metastasis vary, depending on tumor location, surgeon preference, and the patient's overall disease status and associated morbidity. Pain relief in cases of pathological long bone fractures is crucial. The main goals of surgical intervention in these cases include restoring functional stability and mobility, pain control, and improving quality of life. Weight-bearing bones are at high risk of fracture, and are an indication for surgery. Postoperative external beam radiation is recommended in many cases to eradicate residual microscopic disease or tumor progression.[6] As each patient requires individualized care, each bone location requires special consideration regarding the type of fracture fixation to be performed. In general, pathological fractures due to metastatic disease are treated by repairing or removing existing bone. If there is still residual bone with structural integrity, it can be used to insert nails or plates augmented with polymethylmethacrylate. When the host bone is mechanically incompetent, massive bone loss occurs, or joint surfaces are destroyed, the bone is removed and replaced with a prosthesis.[4] Although there is agreement on indications for most fixation methods, there is some controversy about the best treatment for metastatic bone disease.

Controversial areas include the humeral diaphysis, acetabulum, and femoral neck. Some actions are chosen solely based on surgeon preference, while others are chosen

based on experience combined with scientific principles. In addition to predicting patient life expectancy and understanding tumor biology, the different biomechanical properties of different areas of the same bone must also be recognized to achieve the best results.[4] Pathological fractures arising from metastatic disease can jeopardize patient morbidity and mortality. They are painful and affect mobility. Pathological fractures require immediate clinical evaluation and surgery is usually performed under less-than-ideal conditions. The mainstay of clinical management for metastatic bone disease is palliative and aims to improve quality of life, avoiding pathological fractures. Literature reports that patients undergoing prophylactic fixation of metastatic lesions lose less blood in the operating room, have shorter hospital stays, and better function after surgery compared to patients undergoing pathological fracture fixation.

Prophylactic fixation is also reported to prevent complications of pathological fractures, namely delayed union or non-union and the need for reoperation. Therefore, it is important for clinicians to accurately predict the occurrence of pathological fractures or feel at ease when the possibility of fracture does not occur. This ensures that prophylactic fixation is performed only when necessary, and when the benefits of fixation outweigh the risks of major surgery. Mirels developed a scoring system to predict impending fractures. This score has four components: anatomical location, size, radiographic appearance of the lesion, and severity of pain. Each component can be scored from one to three and consequently, the Mirels score ranges from four to twelve. A Mirels score of nine estimates a 33% risk of pathological fracture and surgical intervention is recommended. Although the Mirels score is commonly used in clinical practice, it has some limitations because most of the score components are subjective and prone to variation.[12]

Based on the overall score, recommendations for or against prophylactic fixation of a lesion are given. According to Mirels' recommendations, prophylactic fixation is highly indicated for lesions with an overall score of 9 or more. Lesions with an overall score of 7 or less can be managed using radiotherapy and medication. An overall score of 8 presents a clinical dilemma. The probability of fracture is only 15% and Mirels recommends that the treating physician use clinical judgment in such cases and consider prophylactic fixation.[14]

Fracture		Score
Site	Upper limb	1
	Lower limb	2
	Proximal femur (peri-trochanteric)	3
Pain	Mild	1
	Moderate	2
	Functional (worse on use limb	3
	Sclerotic (blastic, gain of bone)	1
Lesion	Mixed (combination of sclerotic and lytic	2
	Lytic (loss of bone)	3
Ratio of lesion to diameter of bone	<1/3 diameter	1
	1/3-2/3 diameter	2
	>1/3 diameter	3
Total	8 = 15% fracture risk	/12
	9 = 33% fracture risk	

Figure 5. Mirels' Score as a predictor of pathological fracture in metastatic bone disease.

Prognosis

Clinicians treating patients with bone metastasis need to know the patient's prognosis precisely and weigh the benefits of surgery (improving function and controlling pain) against the risk of increased perioperative mortality. Clinical factor-based prognostic assessment tools for patients with

metastatic bone tumors have been developed to accurately predict life expectancy. Willeumier et al. created a prognostic model, OPTModel, from data of 1,520 patients with bone metastasis in long bones who were treated with radiotherapy or surgery between 2000 and 2013.[25] Patients were divided into four categories based on primary tumor, Karnofsky performance score, and the presence of visceral and/or brain metastasis. Median survival was A: 21.9 months (95% confidence interval [CI], 18.7 to 25.1 months), B: 10.5 months (95% CI, 7.9 to 13.1 months), C: 4.6 months (95% CI, 3.9 to 5.3 months), and D: 2.2 months (95% CI, 1.8 to 2.6 months) for the 4 categories (Table 1). Another model is PathFx, a machine learning Bayesian network applicable to patients with bone metastasis in the trunk and limbs. This model includes measurable objective variables (age, sex, primary type, Eastern Cooperative Oncology Group performance status score, presence of visceral metastasis, presence of multiple bone metastases, pathological fracture, hemoglobin count, and lymphocytes), and subjective variables (surgeon's estimate of survival), although it has been reported that prognosis can be accurately predicted without these subjective variables. PathFx has been externally validated in many different patient populations and was recently updated to PathFx version 3.0. Meares et al. compared several models, including the revised Katagiri model, SSG score, Janssen nomogram, and SPRING 13 nomogram, and reported that OPTModel showed the highest accuracy in predicting 12-month (area under the curve [AUC] = 0.79) and 24-month survival (AUC = 0.77) after surgical management, while PathFx was the most accurate in predicting 3-month (AUC = 0.70) and 6-month survival (AUC = 0.70). Similarly, Thio et al. successfully developed a machine learning model that predicts 90-day and 1-year survival in patients with bone metastasis in the extremities.

Variables	**Prediction of Prognosis**											
Clinical profile	Favorable				Moderate				Unfavorable			
Karnofsky	80-100		≤70		80-100		≤70		80-100		≤70	
Visceral/brain metastases	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Category	A	A	A	B	B	B	C	C	C	C	D	D
Median survival	21.9 months				10.5 months				4.6 months			
											2.2 months	

Table 1. Prognostic model for estimating survival in patients with symptomatic long bone metastasis (OPTModel) by Willeumier et al.[25]

Errani et al analyzed 159 patients with bone metastasis in the extremities who underwent surgery and reported that pathological CRP (≥1.0 mg/dL) and primary tumor diagnosis were significant negative prognostic factors for 12-month survival. Breast, kidney, prostate, and thyroid cancers were classified as having a good prognosis, while lung cancer, unknown primary cancer, liver, colorectal, bladder, pancreatic, stomach, esophageal, testicular, tonsil, sarcoma, and melanoma cancers were classified as having a poor prognosis. The probability of surviving 12 months was 89% for group A: good primary tumor prognosis and physiological CRP; 57% for group B: poor primary tumor prognosis and physiological CRP or good primary tumor prognosis and pathological CRP; and 13% for group C: poor primary tumor prognosis and pathological CRP. The main goal of bone metastasis treatment is to improve symptoms and prevent the development of bone-related events. Surgical and/or medical treatment can be determined according to the patient's prognosis. Patients with poor prognosis can be treated with less invasive palliative care. Surgical treatment should be considered if life expectancy is estimated to exceed 6 weeks. Patients with a life expectancy of 3-12 months should be treated with less

invasive surgical reconstruction that does not require long-term rehabilitation.[26]

Patients with a life expectancy of more than 12 months should be treated with en bloc resection of bone metastatic lesions and durable reconstruction, such as megaprosthesis reconstruction, which requires long-term rehabilitation. Resection of bone metastasis is likely to prolong overall survival in patients with renal cell carcinoma and solitary bone metastasis. Ruatta et al. retrospectively investigated 300 patients with bone metastasis from renal cell carcinoma. In multivariate analysis, conformant metastasis was still a predictor of poor prognosis; Memorial Sloan-Kettering Cancer Center risk group, radical resection, and synchronous solitary bone metastasis were predictors of better overall survival.[22]

Tokuhashi et al. initially reported a scoring system for preoperative evaluation of prognosis in patients with metastatic spinal tumors. They revised the scoring system and evaluated treatment outcomes using their strategy. Six factors were included: general medical condition, number of extraspinal bone metastases, number of spinal metastases, visceral metastasis, primary cancer location, and presence of neurological deficit. Each parameter was evaluated with a score, resulting in a maximum total score of 15. Surgical excision was indicated with a total score of 12 or more, while palliative surgery would be recommended with a score of 9 to 11. In patients with a total score of 8 or less, conservative or palliative procedures would be indicated.

Predictive factor	Score (points)
General condition (KPS)	
Poor (KPS 10%-40%)	0
Moderate (KPS 50%-70%)	1
Good (KPS 80%-100%)	2
Numer of extraspinal bone metastases foci	
≥3	0
1-2	1
0	2
Number of metastases in the vertebral body	
≥3	0
1-2	1
0	2
Metastases to the major internal organs	
Unremovable	0
Removable	1
No metastases	2
Primary site of the cancer	
Lung, osteosarcoma, stomach, bladder, oesophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, prostate, breast, carcinoid tumor	5
Spinal cord palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2

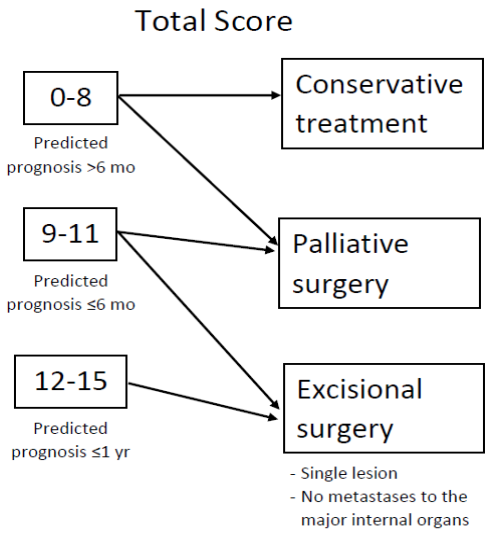

Figure 6. Tokuhashi Score.[7]

CONCLUSION

Palliative management in metastatic bone disease (MBD) focuses on efforts to relieve symptoms, improve functional independence, prevent tumor progression, and improve patients' quality of life. Modern palliative treatment options for MBD patients can be non-operative treatments such as analgesics, radiotherapy, bisphosphonate therapy, denosumab therapy, embolization, high-intensity focused ultrasound (HIFU) as well as palliative operative treatments for cases of metastatic bone disease in long bones and the spine. Prognosis in metastatic bone disease is very important in determining the appropriate choice and type of therapy according to the individual patient's condition.

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