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Medical management of skeletal metastasis

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Bone involvement with tumor has a large impact on quality of life because of the potential for pathologic fractures, spinal cord compromise, hypercalcemia, and pain [1]. Tumor metastases to bone are far more common than primary bone tumors. Although virtually any solid tumor or hematologic malignancy can metastasize to bone, multiple myeloma and cancers of the breast, prostate, lung, kidney, and thyroid are particularly likely to do so [2–8]. Patients with multiple myeloma, metastatic prostate cancer, and breast cancer with bone-only metastases have a prolonged clinical course and may live with skeletal metastasis for several years before succumbing to their disease. Management of the signs and symptoms of bone metastasis in these patients is thus important for maintaining quality of life and mental well-being. Treatment of skeletal metastasis requires input from multiple disciplines, including radiation oncology, neurosurgery, orthopedics, anesthesia, and medical oncology. This article discusses general principles of medical management of bone metastases, including diagnosis and follow-up; management of specific symptoms; options for systemic treatment, including bisphosphonates; specific details about each cancer type; and future directions in therapy.

Diagnosis and follow-up of bone metastases

Bone scintigraphy (bone scan) is more sensitive for detecting bone metastases than plain radiographs and is often performed as part of the initial staging of newly diagnosed cancer. Data show no benefit to routine bone scans in asymptomatic cancer survivors, and bone scintigraphy is generally not recommended. Plain radiographs or bone scans should be performed when patients develop symptoms. Radiographically, bone metastases may be osteolytic, osteoblastic, or mixed. Because bone scintigraphy reflects osteoblastic activity, purely lytic bone lesions may result in a false-negative bone scan. This is often observed in multiple myeloma; in these patients, radiographs of the skeleton are performed for initial staging and at routine intervals to determine response to therapy versus progression of disease.

The location of bone metastases reflects blood flow to the underlying bone. Most solid tumors metastasize to the axial skeleton and proximal long bones. Metastases to the hands and feet are distinctly rare. In men with prostate cancer, tumor emboli are carried through venous drainage to Batson's plexus. In this disease, bone metastases generally present in the pelvis, proximal femur, and lumbosacral spine.

Evaluation of response to therapy for bone metastases can be complex. Osteoblastic activity may increase as bone heals after successful treatment, and the bone scan may initially worsen. Hormonal therapy for breast or prostate cancer can cause tumor flare with temporarily worsened pain and hypercalcemia. Intermediate and long-term improvement in pain, in serum markers (eg, prostate-specific antigen [PSA], CA15-3, alkaline phosphatase), and in the bone scan may be helpful in determining the response to treatment.

Clinical symptoms of bone metastasis

Pain

Poorly managed cancer pain contributes to depression, anxiety, and fatigue [9]. Physicians

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should ask about pain regularly, because patients do not routinely volunteer this information [10]. Increased awareness of pain has led to its classification as the "fifth vital sign." The management of pain is crucial and is discussed in detail elsewhere in this issue. In short, bone pain often responds best to a combination of nonnarcotic analgesics (either nonsteroidal anti-inflammatory agents or acetaminophen given in full doses on schedule) and narcotic analgesics. Long-acting narcotics are recommended if the patient requires more than three or four doses of short-acting opioids per day. Corticosteroids add additional benefit in patients with spinal cord or nerve root compression. For acute management of severe bone pain, localized therapy, such as spinal injections, radiation, or surgical stabilization to painful sites, generally has a faster onset of relief than treatment with systemic therapy [11]. Radiation therapy can contribute to suppression of the peripheral blood counts often seen in patients with extensive bone marrow involvement with cancer and can interfere with subsequent systemic therapy. It should therefore not be used in a cavalier fashion. Nonpharmacologic methods of pain management, including cognitive techniques and acupuncture, also allow patients to gain control over their pain [12].

Hypercalcemia

Hypercalcemia of malignancy may be caused by bone metastases, particularly lytic bone metastases, or by paraneoplastic secretion of parathyroid hormone–related protein. The two conditions may coexist, particularly in patients with breast cancer. The initial treatment is identical to treatment of primary symptomatic hypercalcemia. Many patients present with prerenal azotemia or acute renal insufficiency. Patients should first be evaluated for severity of dehydration and appropriately hydrated. After near-normalization of renal function, patients are treated with an intravenous bisphosphonate, resulting in a nadir of serum calcium in 7 days. Retreatment with an intravenous bisphosphonate is not recommended more frequently than once every 7 days. Corticosteroids are beneficial in multiple myeloma because of the tumoricidal effect of steroids and because of their inhibitory effect on osteoclasts. Successful long-term management of hypercalcemia depends on effective treatment of the underlying malignancy.

Pathologic fractures

Careful physical examination with attention to the spine, pelvis, and hips should be regularly performed on every cancer patient. Weight-bearing bones, such as the pelvis, vertebral bodies, and femur, are most prone to pathologic fractures. The incidence of pathologic fractures can be reduced with careful surveillance and routine follow-up. Although prophylactic intravenous bisphosphonate therapy is not routinely recommended [13], routine radiographs of the femur, humerus, and pelvis should be performed if evidence of metastatic involvement is seen on a bone scan. If bone involvement is also seen on plain radiographs, patients should be given intravenous bisphosphonates every 3 to 4 weeks. Aside from relying on patient history in selecting the area to image, no studies have been proven to assess the risk of pathologic fractures accurately [14].

Systemic therapy of bone metastases

Although local treatments, such as radiation and surgery, have an important role in management of bone metastases, long-term control usually requires systemic therapy. Bone metastases are generally not life threatening, and patients often have a prolonged clinical course. The need to control bone pain should thus be carefully weighed against the toxicity of therapy. Providing effective treatment with minimal toxicity is an important goal.

Hormonal therapy

Most prostate cancer and about 60% of breast cancer are sensitive to hormonal manipulation. Tamoxifen, a selective estrogen receptor modulator, traditionally has been the estrogen agonist/antagonist of choice in breast cancer. Toxicity includes hot flashes, an increased risk of endometrial cancer, and venous thromboembolism. Because of its estrogen agonist effect in bone, bone density is preserved, at least in postmenopausal women. Another class of drugs, the aromatase inhibitors, blocks peripheral conversion of androgens to estrogen [15]. Although aromatase inhibitors are ineffective in premenopausal women, various trials have demonstrated that aromatase inhibitors, specifically letrozole, prolong survival when compared with tamoxifen in postmenopausal women with metastatic disease. Aromatase inhibitors lack the estrogen agonist activity that

tamoxifen exerts in the bones. Thus, osteoporosis is a side effect of this therapy. Other classes of hormonal agents that are sometimes effective in metastatic breast cancer include progestins, androgens, and, occasionally, estrogen. Patients who have a long response to one hormonal agent often respond well to second-line therapy. Response to therapy may take up to 8 to 12 weeks.

Androgen deprivation is the mainstay of hormonal therapy in prostate cancer. Options include surgical (orchiectomy) or medical (GnRH agonists) castration. The GnRH agonist effect may cause a tumor flare because of an initial increase in androgen production. This can be prevented with antiandrogens, such as flutamide. Other hormonal manipulations that are occasionally effective in reducing PSA values and improving bone pain include antiandrogen withdrawal, glucocorticoids, estrogen, and ketoconazole. The median survival for men with hormone-sensitive prostate cancer is several years. Once it becomes refractory to initial hormone therapy, the likelihood of response to subsequent hormonal manipulation is lower than in breast cancer, and the median survival is between 9 and 11 months [16,17].

Chemotherapy

Chemotherapy is usually given to patients with prostate cancer and breast cancer when hormonal agents become ineffective. Breast cancer is often chemotherapy sensitive. The most effective agents are doxorubicin and the taxanes. Other effective agents include capecitabine, which has the advantage of being an oral agent with little myelosuppressive effect. Vinorelbine and gemcitabine are examples of other intravenous chemotherapies. Although prostate cancer has been considered less responsive to chemotherapy, studies in recent years have demonstrated the effectiveness of several combinations of agents, including mitoxantrone and prednisone. Estramustine, a conjugate of estradiol and nitrogen mustard, has been used alone or in combination with vinblastine or taxanes. Regimens used for multiple myeloma include combinations of melphalan and prednisone, high-dose pulse dexamethasone, infusional vincristine/adriamycin, and biologic response modifiers (eg, thalidomide, bortezomib).

Radiopharmaceutic agents

Radioisotopes, such as strontium, are incorporated into bone and can be used systemically to target bone metastases in patients with diffuse bone involvement. Strontium 89 is deposited in calcifying bone and is effective in the treatment of osteoblastic bone metastases. It has been used primarily in prostate cancer, breast cancer, and other cancers with osteoblastic metastases. The major toxicity is myelosuppression [18]. Improvement in pain can be achieved in approximately half of patients. Small studies of combinations of radioisotopes and chemotherapeutic agents demonstrate potential benefit [17,19].

Bisphosphonates

Bisphosphonates are pyrophosphate analogues with a P-C-P bond instead of a P-O-P bond, which are more resistant to enzymatic hydrolysis [20]. Two different bisphosphonate classes are currently available: the nonnitrogen-containing bisphosphonates, also known as the first-generation bisphosphonates, and the nitrogen-containing bisphosphonates, which are divided into the second and third generations of bisphosphonates by differences in their side chains and level of potency. The first-generation bisphosphonate, clodronate, works by a different mechanism of action than the others. It seems to inhibit a mitochondrial adenosine triphosphate translocase, whereas the nitrogen-containing bisphosphonates inhibit farnesyl diphosphate synthase, and effectively blocks prenylation of small guanosine triphosphatases (GTPases) that are involved in cell morphology, motility, and cell invasiveness [21]. Although most of the clinical trials on bisphosphonates have been conducted in patients with metastatic breast cancer and multiple myeloma, small studies of bisphosphonates in patients with other metastatic carcinomas have demonstrated benefit. The duration and timing of therapy have not been thoroughly studied. Experts recommend the use of bisphosphonates indefinitely or until patients deteriorate [13,22].

First-generation bisphosphonates

Although also available in an intravenous form, oral clodronate was the first bisphosphonate to reach clinical trials. Three studies have attempted to determine whether clodronate decreases the development of bone metastases in women with high-risk but nonmetastatic breast cancer. A two-year randomized non–placebo-controlled study showed a decrease of skeletal metastasis and distant extraosseous disease in the clodronate group [23]. The observed benefit of clodronate in treatment group seems to have

decreased with longer follow-up [22]. In contrast, animals treated with bisphosphonates had a decrease in metastatic bone disease but an increase in visceral metastases [24]. Another large 3-year clodronate adjuvant study conducted in patients with node-positive breast cancer showed no decrease in bone or extraosseous metastasis in the treated group, but bone as a first site of relapse was less common [25]. Finally, the most recent adjuvant clodronate study in patients with operable disease demonstrated a decrease in the incidence of bone recurrence and mortality during therapy [26]. Based on the findings in the current literature, guidelines from the American Society of Clinical Oncology and the British Association of Surgical Oncology [27] do not recommend routine treatment of high-risk breast cancer patients with adjuvant bisphosphonates [13].

Second-generation intravenous bisphosphonates

The dose and infusion time of pamidronate, an intravenous nitrogen-containing bisphosphonate, have been extensively studied for efficacy and safety in a large multicenter metastatic breast cancer trial [28–30]. Unlike therapy with radioisotopes or external beam radiation, pamidronate decreases future skeletal events. Given good renal function in a patient, pamidronate can be given safely for at least 24 months [29]. Most complications from pamidronate infusions result from shortened time of infusion [31]. Transient flu-like symptoms, symptomatic hypocalcemia, bone pain, injection site reactions, leukopenia, and thrombocytopenia have been reported [29,30,32]. A three-arm study with intravenous pamidronate, intravenous clodronate loading followed by oral clodronate, and oral clodronate revealed superior pain control with intravenous pamidronate [33].

Third-generation bisphosphonates

Third-generation bisphosphonates include risedronate, ibandronate, and zoledronic acid. These are heterocyclic aminobisphosphonates with about 100-fold higher potency than pamidronate [20]. Risedronate has not been studied for the treatment of skeletal metastasis. Ibandronate, although used in clinical trials, has not shown consistent efficacy for bone metastasis [34]. Zoledronic acid, conversely, has shown greater efficacy than standard dose pamidronate. A large randomized multicenter trial on metastatic breast cancer and multiple myeloma over a period of 12 months demonstrated that zoledronic acid significantly decreased bone events (eg, fracture, need for additional radiation for bone pain) compared with pamidronate [35]. Zoledronic acid also caused a greater decrease in N-telopeptide excretion in treated patients. N-telopeptide is thought to be highly predictive of future skeletal complications and to decrease when patients are responding to bisphosphonate therapy [31,35–40].

In summary, bisphosphonates are approved by the US Food and Drug Administration for use in multiple myeloma and metastatic bone lesions from solid tumors. It is recommended that therapy be initiated in patients with bone metastases evident on plain radiographs [22]. The use of bisphosphonates in patients with bone metastasis only evident by bone scan is not recommended [22]. Current studies do not provide evidence to show superiority of one intravenous bisphosphonate over another [31,35].

Specific tumor types

Breast carcinoma

Approximately 200,000 women develop breast cancer in the United States each year. Thirty percent of patients with breast cancer develop metastatic disease (Table 1). Bone metastases are the most common initial site of metastases. Most patients with metastatic breast cancer eventually die of metastases to parenchymal organs. Patients with bone-only metastases may survive for several years. This is particularly true for tumors that express hormone receptors [41–43]. Because of the long median survival after development of bone metastases, patients are at high risk for skeletal complications [21]. The likelihood of hormone responsiveness is based on hormone receptor status and site of metastases. Bone, soft tissue, and nodal metastases are much more likely to respond to hormonal manipulation than lung and liver metastases. A prolonged response to a hormonal agent predicts a good response to a second agent. Chemotherapy is used when the tumor becomes hormone refractory. Bone metastases in breast cancer are osteolytic and osteoblastic (Fig. 1). This vicious cycle may be interrupted with bisphosphonates, which prolong the time to the first skeletal complication and improve survival [30,44].

Prostate carcinoma

Prostate cancer is a common malignancy that affects aging men (see Table 1). African-American men tend to have a more aggressive course than

Table 1
Comparison of breast, prostate, lung cancer, and multiple myeloma

Cancer site	Breast	Prostate	Lung	Multiple myeloma
SEER incidence (per 100,000)	130	150[a] 100[b]	60	8–10[a] 4–5[b]
Patients with bone metastasis at time of death (%)	70 [2]	85–100 [57,58]	20–40 [59]	100
Radiographic appearance	Mixed lytic and blastic	Blastic [39,60]	Mixed	Lytic
Mean survival after bone metastasis diagnosed	2 years	32 months if hormone sensitive, 11 months if hormone refractory	3–9 months	3–4 years
Systemic therapy	Hormones, chemotherapy, bisphosphonates	Hormones, chemotherapy, bisphosphonates, radiopharmaceuticals	Chemotherapy, ?bisphosphonates	Chemotherapy, biologic agents, bisphosphonates

Abbreviation: SEER, surveillance, epidemiology, and end results.
[a] African American.
[b] White.

white men. This is thought to be secondary to androgen receptor microsatellite and polymorphism differences between white and African-American men [45,46]. At least 95% of hormone-refractory prostate cancers are metastatic to the bone [47]. Unlike other malignancies, many men die from metastatic prostate cancer with bone as the only metastatic site [19]. Prostate cancer, even more so than breast cancer, responds to hormonal therapy and specifically to androgen deprivation. Chemotherapy has not been commonly used until recently, when several combinations of chemotherapy have been found to have response rates is the range of 30% to 50% with acceptable toxicity.

Prostate cancer metastases are typically osteoblastic. Spinal and cranial nerve root compression can result from narrowing of neural foramina from proliferation of dense but brittle bone. Combinations of radioactive strontium and various chemotherapeutic agents have suggested improved survival in patients treated with the combination [19]. These trials are difficult to interpret because they contain small numbers of patients and results may reflect a patient selection bias. Bisphosphonates not only treat skeletal metastasis in prostate cancer patients but help to reduce the pain and fracture risk associated with osteoporosis induced by chronic androgen deprivation [48].

Lung carcinoma

Lung cancer is still the leading cause of cancer mortality in the United States (see Table 1). The median survival of patients with metastatic bone disease is reportedly between 3 and 9 months, and most patients die of progressive disease before skeletal complications become a large problem [49]. Bisphosphonates have not been explicitly studied in metastatic bone disease from lung cancer, probably as result of inadequate accrual and short follow-up. Of the 66 enrolled in an oral clodronate study of cancers, including non-small cell lung cancers, that had responded poorly to chemotherapy, only a few patients were alive for evaluation at the end of a year [50].

Multiple myeloma

Multiple myeloma is a B-lymphocyte disorder accounting for approximately 10% of hematologic malignancies (see Table 1). Osteolytic bone disease is included in the staging criteria of myeloma, although patients may also present with solitary plasmacytomas without evidence of systemic involvement. Most patients with multiple myeloma die of infections or renal failure, but bone pain is usually the first manifestation of disease. Skeletal complications are the predominant clinical feature. Bisphosphonates play an integral role in the therapy of patients with

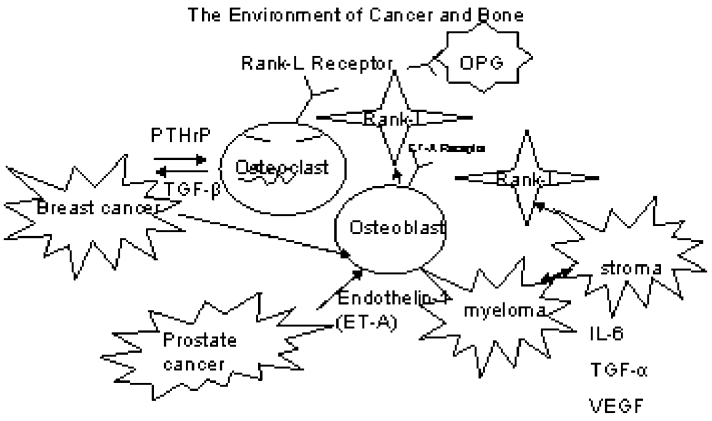

Fig. 1. The environment of cancer and metastatic disease. (*A*) Breast tumor cells in the bone release parathyroid hormone–related peptide, which signals the osteoclasts to resorb bone and to release tumor growth factor-β (TGFβ). TGFβ is then stored in the bone matrix and acts as a growth factor for tumor cells and the surrounding stroma. Osteoblasts secrete receptor activator for nuclear factor-κβ ligand (RANK-L), which signals osteoclasts to resorb more bone after activation by tumor cells [38]. (*B*) In vitro models suggest that prostate tumor cells secrete endothelin-1, which binds to osteoblast receptor ET-A and leads to tumor growth. This osteoblast growth and differentiation effect was cell specific, because another prostate cancer cell line did not show the same effect [55]. (*C*) Myeloma cells and stromal bone marrow cells secrete various cytokines, such as interleukin-6, TGFα, and vascular endothelial growth factor, which sustain the continued proliferation of tumor and stromal cells. In the normal bone environment, cross-talk between osteoblasts and osteoclasts maintains a balance between bone formation and breakdown [56]. Osteoblasts and stromal cells release RANK-L, which, in turn, binds to receptors on osteoclasts and signals bone resorption. Osteoprotegerin is a soluble decoy receptor, which binds to excess ligand and prevents activation of osteoclasts.

multiple myeloma. Although bisphosphonates have not changed the overall survival of patients with myeloma, they certainly improve quality of life. In some mouse models, they decrease serum paraprotein levels [51].

Multiple myeloma is a model disease for rapid translation of bench research into clinical therapeutics. Various novel targets have come about from the understanding of the interaction of myeloma cells and their stromal environment (see Fig. 1).

Novel therapy

Translational research has been challenging in this field because few animals spontaneously develop cancers that metastasize to the bone. Existing bone metastasis animal models have been developed in the laboratory by either artificially implanting xenografts into bone or by diverting the normal metastatic pattern so that bone metastasis can occur [52].

New targets of skeletal metastasis have been identified from work in the basic science area. One of the up and coming targets is that of the receptor activator for nuclear factor-κβ receptor on osteoclasts. Various methods of inactivation of this receptor have been performed in animal studies [51,53]. One promising drug, AMGN-0001, a recombinant osteoprotegerin, has been shown to decrease N-telopeptide excretion in a phase I trial conducted in patients with metastatic breast carcinoma or multiple myeloma [54]. Animal studies with the parathyroid hormone–related peptide (PTHrP) antibody are also encouraging [55]. A humanized monoclonal PTHrP antibody is in early clinical trials [44].

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