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Review Paper

Bone metastasis in breast cancer

Richard L Theriault[CA] and Gabriel N Hortobagyi
The authors are at the Department of Medical Oncology (Breast Medical Oncology), The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Fax: (713) 794-4385.

Bone metastases in breast cancer are common and frequently lead to serious skeletal related morbid complications. Metastases develop in areas of metabolically active trabecular bone. It is presumed that breast cancer cells undergo the same stepwise process for metastases development as demonstrated in other tumor types. The specific factor or factors responsible for the osteotropism of breast cancer have not been identified. The morbid events associated with skeletal metastases, such as pathologic fracture, and spinal cord compression, may be assessed objectively by a variety of techniques including skeletal radiography, radionuclide scanning, computed tomographic scanning and magnetic resonance imaging. Biochemical parameters or markers of skeletal metastases are not sensitive enough to detect clinically occult disease. Therapeutic interventions for bone metastases include local and systemic therapies. Surgery and radiation therapy are most frequently used for relief of pain or impending fracture, or when bone fracture or neurologic compromise has already developed. Systemic treatment of bone metastases appears to be as effective as systemic treatment of other metastatic sites. Both hormone and chemotherapy may provide significant palliation. Clinical research suggests that the adjunctive use of bisphosphonates may significantly reduce the incidence of skeletal-related morbid events associated with osteolytic bone disease. Future research efforts directed at determining the osteotrophic factors responsible for bone metastases in breast cancer, the pathophysiology of the bone remodeling process in metastatic disease and the prophylactic use of bisphosphonates may lead to significant clinical benefit for those in whom bone metastases from breast cancer develop.

Key words: Bone, breast cancer, metastasis.

Introduction

Breast cancer is the most common malignancy in women in the US. Of the 180 000 newly diagnosed breast cancers in 1992, about one-third will eventually metastasize and cause death.[1] Although metastases can develop in any organ system, lung, liver and bone are the most frequent sites of disease, exclusive of lymph node metastases.[2–4] Bone is the most common first site of metastases from breast cancer.[5–7] Bone metastases represent a formidable clinical problem which may result in considerable skeletal related morbidity from bone pain, fracture, spinal cord compression or hypercalcemia.

Metastasis development

The development of metastases is a complex process involving tumor cell and host.[8] In order for neoplastic cells to metastasize they must first broach endothelium and invade vascular and/or lymphatic spaces.[9] Not all cells of malignant phenotype have the capacity to undergo the metastatic process. Once in circulation, few cells survive the transport to other organ sites; however, those that do become arrested in the microcirculation. Although mechanical factors may contribute to the metastatic process, adhesion molecules, such as the integrin family of glycoproteins, are felt to be important in establishing micrometastatic sites.[10]

Invasion at metastatic sites requires dissolution of basement membranes, a process facilitated by tumor cell production of degradative enzymes.[9,11–13] Proteases, such as cathepsins and metalloproteinases, appear to have significant roles in the development of metastases. The clinical observation, in a variety of tumor types, that certain metastatic patterns are common suggests that organ derived factors may be important in establishing new disease sites.[14,15] Local factors produced by the tissues in which tumor cells arrest may promote the growth of the new metastatic sites. The specific factor or factors which result in the high frequency of skeletal metastasis in breast cancer are yet to be identified (Table 1). A variety of bone derived factors have

[CA] Corresponding Author

Table 1. Bone destruction and tumor metastasis: potential factors for osteotropism

Mechanical/vascular factors
Adhesion molecules
Growth factors (TGF-β)
Chemotactic factors
Enzymes—tumor cell derived
Osteoclast activating factors, e.g. prostaglandins and parathormone-like peptide

been postulated as facilitators of the metastatic process. Growth factors, such as transforming growth, factor-β (TGF-β), can stimulate tumor cell growth and resorbing bone has been shown to stimulate tumor cell growth as well as potentiate tumor cell invasion and metastasis development. Chemotactic factors derived from resorbing bone may act as attractants for tumor cell deposition and growth.[15,16] A wide variety of tumor cell products have osteoclast activating activity and such bone resorbing activity induced by local tumor cell adherence may facilitate tumor cell growth.[17] It is well established that a variety of growth factors for hematopoietic cells are produced within the trabecular bone and marrow compartments. It is not clear what role these microenvironmental growth factors have in facilitating breast cancer bone metastases. Consistent and relevant *in vitro* or *in vivo* bone metastases models for breast cancer need to be developed.

Bone remodeling

Bone is a metabolically active organ system which undergoes constant remodeling, not only during the period of growth and development, but also in the mature individual. Remodeling begins with osteoclast activation and is followed by osteoblast formation of new bone. The specific signal(s) which induce osteoclast activity may be osteoblast derived.[18,19] The osteoclast attaches to bone surfaces where it forms an acidic cell-surface junction. The osteoclast proton pump maintains the acidic environment necessary for lysosomal activation and bone dissolution. Osteoclasts, derived from the monocyte-macrophage cell-line, differentiate and proliferate in response to macrophage colony stimulating factor, and are mobile cells within the confines of bone.

The osteoblast, derived from marrow stromal cells, provides for new bone formation and repair of areas of osteoclast dissolution. A number of osteoblast derived proteins, such as osteocalcin and osteopontin, are important for new bone formation.[20,21] In addition to local factors, hormones, especially estrogens and corticosteroids, have a profound influence on bone integrity.[22,23]

Trabecular bone, the most metabolically active site of bone remodeling, is the most frequent location of the metastasizing breast cancer cell. Metastases develop most often in the axial skeleton, especially in the pelvis, spine and ribs. While the skull, proximal femora and humeri may be involved, more distal bony sites for metastases are less frequent.

Clinical manifestations of bone metastases

Once established, metastatic bone disease will ultimately cause symptoms. Pain is the most common presenting problem and is usually localized to the area of bony involvement. The mechanism of pain may be related to tumor involvement of periosteum, bone fracture, local factors produced by the tumor cells (such as prostaglandins), muscle contraction, or nerve root or spinal cord compression. In a series of breast cancer patients with bone metastases, pathologic fracture, spinal cord compression and hypercalcemia were the most debilitating consequences of bone disease.[24] The time course for development of these complications in patients with bone only metastases varied from 11–17 months. Bone metastases are often associated with metastases at other body sites; however, in those patients with bone only metastases the prognosis may be more favorable.

Detection of bone metastasis

The desire to prevent or ameliorate skeletal related morbidity provides the impetus for detecting bone disease before it becomes clinically manifest. There are no good laboratory tests for bone metastases detection. Alkaline phosphatase has not been shown to consistently reflect bone metastases disease activity and may be normal in a significant proportion of patients with bone metastases.[25] Hydroxyproline may be abnormal in bone disease, but is influenced by factors other than metastases, including diet and age. It also lacks consistency in reflecting bone disease regression or progression.[26–28] Pyridinoline and deoxypyridinoline have been suggested as more accurate markers for reflecting the presence of bone

metastases in breast cancer.[29] The reported abnormalities of hydroxy pyridinium in metabolic bone disease may curtail the utility of these measurements in bone metastases.[30]

Serial measurement of osteocalcin may also reflect bone metastasis disease activity, particularly in blastic disease.[31] Osteocalcin has an inverse correlation with bone lysis and has been reported to be present at higher levels in patients with bone metastases than in those with visceral disease.[32] Its utility as a biologic marker is not yet well defined.[33,34]

Characteristic distribution patterns of detectable metastases may be seen with both skeletal radiography and scanning techniques. Skeletal radiography, particularly of areas of bone pain, may demonstrate metastases; however, it is estimated that 50% of cortical bone must be focally destroyed before lytic metastases will be apparent.[25,35] The specificity of abnormal findings on radiography is high. The majority of skeletal metastases from breast cancer are lytic, with mixed lytic/blastic and pure blastic change in decreasing frequency.[24,25] Disease that appears radiographically to be purely lytic may be shown to have a blastic component by histologic evaluation or bone scan. Lytic disease usually appears as an area of decalcification and cortical bone loss, but may occasionally be represented by diffuse osteopenia.[24]

Radionuclide bone scanning is a more sensitive technique for detecting abnormal osteoblastic activity than radiographs, but much less specific. Most metastatic lesions will be visible by bone scan techniques; however, a higher false-positive rate is seen coincident with the high detection sensitivity.[25,35] Bone scan images of metastases are usually multiple, of irregular contour and generally in the axial skeleton. Diffuse bone metastases may result in markedly increased radionuclide uptake leading to a 'super scan'. Suspicious areas of abnormality on bone scan may be confirmed by conventional radiography, or require alternate confirming procedures such as computed tomography (CT) scan, magnetic resonance imaging or biopsy. CT scanning of affected bone metastatic sites has been reported to be more sensitive for detection than radiography and to be more accurate in response assessment.[36]

Magnetic resonance imaging images marrow within the trabecular spaces, particularly of lumbar/and thoracic vertebrae. While abnormal signal intensity may confirm the clinical suspicion of metastases, isolated abnormalities will require histologic confirmation or serial evaluation over time.[37]

The role of imaging procedures, especially bone scanning, in the asymptomatic patient is not well defined either in the preoperative assessment or long-term follow-up setting.[38,39] The utility of 'early' detection of bone metastases has been questioned because of the lack of demonstrable survival benefit in those with early versus late diagnosis. Studies assessing skeletal related morbid events in patients with early versus later detection of bone metastases are yet to be done. Whether significant benefit might be derived from earlier intervention for bone disease is unknown. Prevention of catastrophic complications, such as pathologic long bone fracture or spinal cord compression, is possible with early diagnosis.

Response assessment for treated bone metastases

The response assessment of treated bone metastases is difficult and frought with uncertainty. Clinical response may be manifest by pain relief, improved performance status and the patient/physician assessment of simply 'being' better.

Healing, as demonstrated radiographically, may manifest in a variety of ways.[25,40] Recalcification of lytic lesions may occur or new blastic areas may develop in previously radiographically normal bone.[41] Blastic areas may become more dense or fade and a seemingly normal bone architectural pattern may reappear.

Skeletal radiography is more accurate than radionuclide scanning in response assessment. Response determination by bone scanning is difficult and unreliable because of increased blastic activity and 'worsening' of bone scans in responding patients. Bone scan 'flare' has been reported as a source of error in response assessment, but also a predictor of success for systemic therapy.[42,43] Bone scans may return to normal or the areas of previous disease fade as the intensity of osteoblastic activity decreases.

CT scanning may be of value in assessing cortical bone reconstruction, particularly in areas not readily assessed radiographically such as the skull and vertebral pedicles.[44] The role of magnetic resonance imaging in bone response assessment is not defined.

Therapy of bone metastases from breast cancer

Bone metastases respond to systemic therapy as well as other metastatic sites.[25] The choice of systemic

therapy depends on the location of the disease hormone receptor status, antecedent treatment, other vital organ damage and inherent risks of the therapeutic choice. Bone only metastases have been reported to have a more favorable prognosis and an 'indolent' course.[45,47]

It has been suggested that hormone receptor positive cancers more frequently metastasize to bone.[48,49] A number of hormone therapies may provide clinical benefit by relieving pain and improving function. Tamoxifen is generally a first-line treatment because of its tolerability and low toxicity profile. Additive hormonal therapy may be associated with tumor flare within the first few days of treatment.[50] During this time, bone pain may increase significantly and severe hypercalcemia may develop. Tumor flare has been reported, anecdotally, to predict for tumor hormonal responsiveness. Tumor flare should not be a cause for premature discontinuation of hormonal therapy. Patients can be supported with analgesic medication and low dose corticosteroids while therapy continues. Careful monitoring of serum calcium levels will allow early intervention and prevention of the development of severe hypercalcemia. Hormone therapy may provide a 30% response rate in unselected patients and up to 70% of patients with estrogen/progesterone receptor positive tumors may respond.[51,52]

Systemic chemotherapy is commonly employed in hormone unresponsive tumors and in those tumors unlikely to respond to hormones, such as hormone receptor negative tumors. A variety of chemotherapy regimens have been used, with multiple drug regimens having the highest response rate. The commonly used combination of fluorouracil, doxorubicin and cyclophosphamide has been shown to result in response for approximately 70% of patients with breast cancer metastases. In bone only metastases, the objective response rate is reported to be 59% with 7% complete remissions.[24] Although a number of authors have reported[53–55] bone metastases to be less responsive to chemotherapy (Table 2), these differences may reflect the difficulty of response assessment rather than an inherent biologic difference of bone metastases (Table 3). Overall the response of metastatic disease in bone is not different than for other disease sites.[56–58] Tumor response to chemotherapy is independent of hormone receptor status.

Table 2. Chemotherapy of breast cancer response in osseous metastases[a]

Reference	All patients		Osseous metastases	
	N	CR + PR (%)	*N*	CR + PR(%)
53	68	53	44	41
54	34	56	19	0
55	31	50	16	44
56	619	64	59	63
57	59	64	22	86
58	51	78	25	84

[a] CR, complete response; PR, partial response.

Table 3. Bone response criteria

Complete response
complete recalcification of lytic or mixed lesions
blastic lesions unchanged or reduced in size
bone scan normal or substantially improved
patient asymptomatic
Partial response
some recalcification of lytic or mixed lesions
no new lytic lesions
bone scan stable or improved
symptomatic improvement
Stable
no change in number or size of lesions
no new lesions
bone scan stable
Progression
any new lytic lesion
new blastic lesions after 6 months of therapy

Local therapy of bone metastases

Local measures to treat bone metastases are limited in scope and benefit (Figure 1). The indications for therapy include bone pain, prophylaxis for 'impending' pathologic fracture, fixation of bone fractures and spinal cord or nerve root compression.[59] In a prospective study of radiation therapy for bone pain palliation, patients with breast and prostate cancer were reported to fare better than other tumor types.[60] No difference in response rate for pain relief has been shown for low- versus high-dose radiation.[61] Criteria for impending fracture of bone metastases vary; however, the scoring systemic developed by Mirels is reported to be helpful.[62]

A retrospective study of 59 breast cancer patients treated with radiation therapy for bone metastases reported pain relief and improved performance status in all patients.[63] Radiographic evidence of bone healing was seen in one third of those treated. Systemic administration of radioisotopes has also

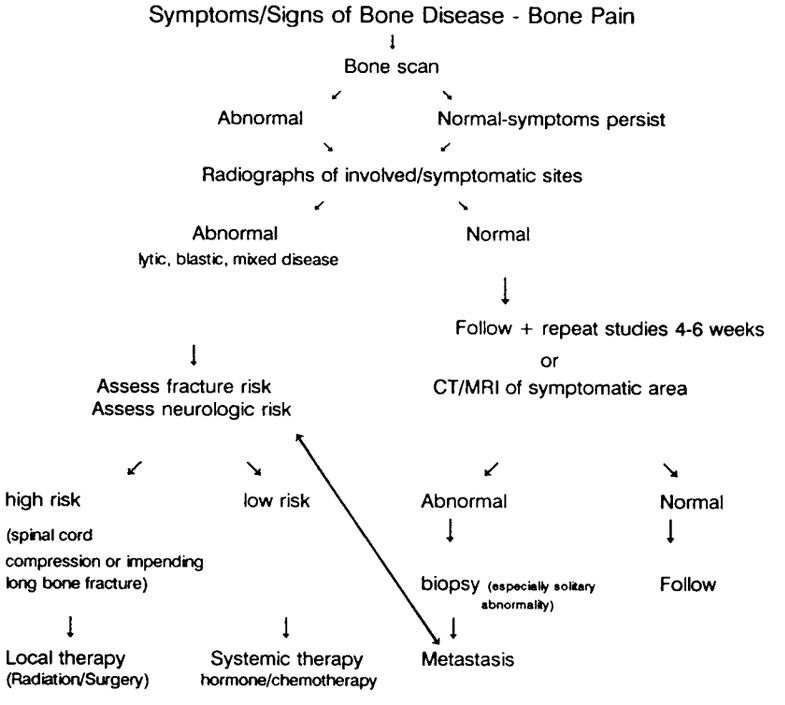

Figure 1. Diagnosis and treatment of bone metastases.

been reported to relieve bone pain. Radioactive phosphorus has been used in breast and prostate cancer, but is not a part of the current treatment armamentarium.[64] Strontium-89, which concentrates at metabolically active areas of bone, has been shown to provide pain relief for many patients.[65–67] Large studies of therapy in breast cancer patients as a distinct group are lacking and strontium use is limited by myelotoxicity. Samarium-153 has also been studied in painful bone metastases.[68] A recent study reported 68% of patients to have had improvement in bone pain after treatment with samarium.[69] This study included only five patients with breast cancer. Treatment related myelotoxicity included anemia, leukopenia and thrombocytopenia.

Surgery is most frequently used for the treatment of long bone metastases and femoral fractures. The goals of relieving pain and restoring mobility may be accomplished by a variety of surgical techniques. Prophylactic surgical fixation for lytic bone disease of the femur has been recommended for lesions of the cortex more than 2.5 cm in size, lesions involving more than 50% of the bone diameter or those that are painful despite prior radiation treatment.[70,71] Immobilization without surgical intervention provides pain relief and healing may occur with local radiation treatment; however, patient mobility is most rapidly restored with surgical correction/repair of long bone fractures. True healing of metastatic bone fractures is a prolonged process. Fifty percent of patients may not heal within 6 months.[72] Epidural spinal cord compression is an oncologic emergency often heralded by increasing pain in a patient with known vertebral metastases. Early diagnosis is the key to maintaining neurologic function. A retrospective report suggests that a combination of surgery and radiation for spinal cord compression yielded better functional results.[73] Once neurologic deficit is present, surgery is rarely done and functional improvement is unlikely.[73] If a neurologic deficit is present, less than 50% of patients will be ambulatory regardless of the type of treatment.[74] Other studies comparing surgery plus radiation with surgery only for pain relief and preservation of neurologic function have shown no difference in patient's functional ability.[74,75]

Hypercalcemia and bone metastases

Hypercalcemia is a common complication of bone metastases but may also occur in patients without bone disease.[78,79] With the availability of antiosteoclast therapy to supplement non-specific measures such as intravenous hydration most hypercalcemic episodes can be controlled.[78] Osteoclast inhibition by calcitonin is rapid and associated with minimal toxicity. It is a good first choice for those with severe hypercalcemia.[80,81] Gallium nitrate and bisphosphonates are effective antiosteoclast therapy for hypercalcemia of malignancy and response rates of 80–100% have been reported.[82–85]

Breast cancer and bone health

In addition to bone metastases a variety of therapeutic interventions have the potential to adversely effect bone health. Adjuvant tamoxifen appears to have a favorable effect on bone manifest by preservation of lumbar spine bone mineral density.[86] Little is known about the bone effects of systemic adjuvant chemotherapy or chemotherapy-induced menopause. Bone loss after surgical oophorectomy is well recognized;[87] however, the treatment related risk of osteoporosis development is just now being assessed in women treated with adjuvant chemotherapy.

The risk of metastases in osteoporotic bone compared to healthy bone is unknown. Is the estrogen sensitive trabecular bone compartment more accessible to metastasizing breast cancer cells? Are me tastasizing hormone receptor-positive cells provided with a friendly microenvironment by factors attempting to maintain the trabecular integrity of osteoporotic bone? For women with a history of breast cancer, are there effective non-hormonal interventions to maintain bone health?

Bone directed therapy in breast cancer skeletal metastases

The use of anti-osteoclast therapy for bone metastases has been supported by reports of reduced morbidity with bisphosphonate therapy. Skeletal related events, including bone pain, pathologic fractures and hypercalcemia, were reported to be significantly reduced in APD treated breast cancer patients.[69,70] This effect was independent of the type of specific antitumor therapy provided. Morton *et al.*[71] have reported sclerosis of lytic bone metastases with treatment with intravenous APD. Clodronate has also been reported to decrease skeletal morbidity from breast cancer bone metastases in a placebo controlled, randomized trial of 173 patients.[72] The bisphosphonates are promising as adjunctive therapy to other local and systemic measures for the treatment of bone metastases. Based on clinical and laboratory observation, they may have a role as preventive therapy for tumor metastases-induced osteolysis.[73] Well designed and carefully controlled clinical trials will be needed to determine the role, if any, of the adjunctive use of bisphosphonates in women with bone metastases.

The study of bone and bone metastases in breast cancer is an area of research which holds much promise for the prevention of metastases and treatment related complications. Improved understanding of bone physiology, those factors which predispose to bone metastases and adjunctive therapies for prevention may significantly impact on the morbid complications of breast cancer bone metastases.

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