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Metastasis and bone loss: Advancing treatment and prevention

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Abstract

Tumor metastasis to the skeleton affects over 400,000 individuals in the United States annually, more than any other site of metastasis, including significant proportions of patients with breast, prostate, lung and other solid tumors. Research on the bone microenvironment and its role in metastasis suggests a complex role in tumor growth. Parallel preclinical and clinical investigations into the role of adjuvant bone-targeted agents in preventing metastasis and avoiding cancer therapy-induced bone loss have recently reported exciting and intriguing results. A multidisciplinary consensus conference convened to review recent progress in basic and clinical research, assess gaps in current knowledge and prioritize recommendations to advance research over the next 5 years. The program addressed three topics: advancing understanding of metastasis prevention in the context of bone pathophysiology; developing therapeutic approaches to prevent metastasis and defining strategies to prevent cancer therapy-induced bone loss. Several priorities were identified: (1) further investigate the effects of bone-targeted therapies on tumor and immune cell interactions within the bone microenvironment; (2) utilize and further develop preclinical models to study combination therapies; (3) conduct clinical studies of bone-targeted therapies with radiation and chemotherapy across a range of solid tumors; (4) develop biomarkers to identify patients most likely to benefit from bone-targeted therapies; (5) educate physicians on bone loss and fracture risk; (6) define optimal endpoints and new measures of efficacy for future clinical trials; and (7) define the optimum type, dose and schedule of adjuvant bone-targeted therapy.

Keywords

Metastasis; Bisphosphonate; RANK; Bone targeted; PTHrP; Bone loss; Denosumab; Zoledronic acid

Introduction

Despite the improvements in screening, early diagnosis and cancer treatments, death from cancer remains the major cause of mortality worldwide. New therapeutic strategies based on improved understanding of cancer biology, targeted treatments and personalized therapies are urgently needed. The success of future therapeutic options is likely to target key interactions between cancer cells and a range of host cells within the bone microenvironment. Bone targeted treatments have the potential to prevent not only bone metastasis but also to impair the ability of tumor cells to remain dormant. We need to realize this potential through relevant preclinical research, high quality clinical trials and improved understanding of cancer and bone cell biology. Priorities were identified in basic and preclinical research, clinical assessment of bone-targeted therapies and physician education.

Pathological complications of bone metastasis

Influence of the bone microenvironment on growth of tumor cells in bone

When tumor cells are resident in bone, they change their patterns of gene expression and modify their phenotype. These changes may lead to important interactions with the normal host cells, not only with other bone cells, but also with primitive hematopoietic (stem) cells and other cells abundant in the bone microenvironment. It is proposed that one of the major factors responsible for this change in behavior is the physical microenvironment the tumor cells experience when they encounter the hard surface of bone. These changes may greatly influence the progression and further aggressive behavior of the tumor.

Preclinical models have shown that PTHrP is one of the factors responsible for tumor osteolysis and can be used as a marker for osteolytic factor production by metastatic cancer cells.[1] PTHrP is also a regulator of the Hedgehog pathway in breast cancer cells, and may be the crucial event in activating this pathway in the bone microenvironment via exposure to TGFβ or via the stiffness of the bone matrix itself.[2] Recent data have suggested that bone has a tissue modulus that is approximately 5–6 orders of magnitude stiffer than soft tissue extracellular matrix (ECM). The high mineral content of the bone ECM makes it more resistant to proteolytic degradation by enzymes secreted or induced by tumor cells than soft tissue ECM.[3] The effects of the physical microenvironment on tumor cell behavior represent an important understudied area of research.

DKK1 and other Wnt signaling antagonists in multiple myeloma

The Wnt pathway has been shown to play an important role in regulating normal bone turnover. Studies have demonstrated that myeloma cells isolated from the bone marrow of multiple myeloma patients express the soluble Wnt antagonist dickkopf-1 (DKK1).[4] Recent preclinical studies have shown that treating mice implanted with primary myeloma cells or 5T2MM murine myeloma cells with an anti-DKK1 antibody prevented myeloma-induced suppression of osteoblast numbers.[5,6] This resulted in increased bone formation and an increase in bone mass. Interestingly, the antibody to DKK1 had no effect on osteoclasts in the studies in the 5T2MM model.

Additional studies have shown that lithium chloride or selective inhibitors of glycogen synthase kinase-3 also prevented osteoblast suppression and the inhibition of bone formation

in the experimental models of myeloma.[7] Taken together, these data suggest that blocking DKK1 or other mediators of osteoblast suppression in myeloma, could be an important new strategy to prevent myeloma bone disease. At least in some studies this was associated with an anti-myeloma effect in bone. Additionally, the possible effects on the endosteal osteoblastic niche may be important in regulating the early development of myeloma.

Bisphosphonates in metastasis prevention – preclinical models

Recent preclinical data suggest that nitrogen-containing bisphosphonates (BPs) can decrease the release of tumor-promoting growth factors from bone and delay skeletal tumor growth by inhibiting osteoclast-mediated bone destruction.[8,9] Further, nitrogen-containing BPs may also inhibit tumor cell functions including adhesion, migration, invasion and proliferation as well as increasing tumor cell apoptosis through inhibition of farnesyl diphosphate synthase (FPPS). Frequent low dose treatment of tumor-bearing animals with nitrogen-containing BPs may result in more prolonged exposure of cancer cells to the drug, enabling a greater direct anti-tumor effect.[10,11] Nitrogen-containing BPs may also potentially be anti-angiogenic.[8,9] Thus, it is possible that frequent administration of low doses of nitrogen-containing BPs to patients with bone metastases might be more appropriate than current high-dose regimens.

Other strategies for metastasis prevention – preclinical models

RANKL, PTHrP, TGF-β receptor antagonists and cathepsin K inhibitors have been used successfully in preclinical models of breast and lung cancers to block bone metastasis.[1,12–22] In addition, blocking Src kinase activity, which plays an important role in osteoclastic bone resorption, also decreased breast cancer bone metastasis.[23,24] Another approach postulated to decrease bone metastasis would be the use of integrin antagonists. For example, a non-peptide integrin αvβ3 antagonist, PSK1404, and antibodies to α_6 integrin inhibit invasion and adhesion of tumor cells, respectively, in the bone microenvironment.[25] In models of osteoblastic bone metastasis in breast cancer, blocking osteoblast activity using an endothelin A receptor antagonist has also been successful in decreasing tumor burden[26] with the majority of studies showing that treatment prior to tumor cell implantation is superior to therapeutic regimens initiated at later stages.[27] Thus, a variety of agents has been shown to block bone metastasis and decrease tumor burden in preclinical models.

Relationship between bone formation or resorption and angiogenesis

Recent studies have suggested that both osteoblasts and osteoclasts can stimulate angiogenesis. Wang et al. have reported that osteoblasts produce VEGF in response to hypoxia thereby coupling angiogenesis and bone formation. The hypoxia-inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development.[28] Cackowski and coworkers have reported that osteoclasts are also important for angiogenesis in bone.[29] These results suggest that in addition to secreting and releasing growth factors that can stimulate tumor growth, bone cells can also enhance angiogenesis in bone to further increase tumor growth and survival. Studies on the contribution of bones cells to the enhanced angiogenesis present in bone metastasis should identify additional beneficial effects of bone-targeted therapy on inhibition of tumor growth in bone metastasis.

Priorities for future research

The following research priorities are proposed to address critical gaps in our understanding of the pathology of metastasis:

- Further study of the physical effects of the bone microenvironment on tumor growth and tumor cell gene expression, including the temporal development of bone metastases.

- Determine if mature osteoblasts can inhibit tumor growth, and explore the effects of targeting osteoblasts and/or osteoblastic lesions.
- Continue to develop syngeneic animal models of bone metastasis.
- Conduct preclinical studies of combinations of bone-targeted therapies. Focus on agents that have different mechanisms of actions, such as anti-resorptives and anabolic agents to assess added or synergistic effects on bone metastasis.
- Determine whether anti-tumor effects of bisphosphonates observed in preclinical models are achieved through direct or indirect effects on tumor cells.
- Utilize preclinical models to study combination therapies targeting both the tumor and bone microenvironments.
- Study the effects of new therapies on cells that may play a role in tumorigenesis and immune response, such as macrophages, myelosuppressor cells and T cells.
- Develop novel technologies to image and study small numbers (1000–2000) of tumor cells and how they locate to specific areas of bone, interact with resident host cells and respond to therapy.

Developing therapeutic approaches to prevent metastasis

Several randomized clinical trials suggest that BPs may prevent not only the development of bone metastases but also extraskeletal metastases and locoregional recurrence. The mechanisms underlying these observations are uncertain but may include a silencing and suppressive effect on dormant micrometastases in the bone marrow that, with conventional therapies only targeting the tumor cell, remain able to seed to extra-skeletal sites. Several small trials have evaluated the impact of monthly dosing of zoledronic acid (ZA) on disseminated tumor cells (DTCs) in serial bone marrow aspirates, as a surrogate for response. All have shown reduction in DTCs in patients receiving ZA.[30–32]

The promising, yet somewhat contradictory, results of three reported adjuvant clodronate studies suggest that BPs can impact disease recurrence, but highlight the need for further investigation. [33–36] A meta-analysis using 5-year data from the clodronate trials did not show a statistically significant difference in overall or bone metastasis-free survival when the data were pooled.[37] However, there was marked heterogeneity among the trials and, by today's standards for adjuvant studies, the trials were too small to provide reliable evidence.

Results from several large adjuvant trials evaluating the role of zoledronic acid are emerging. The ABCSG-12 study investigated the adjuvant use of ZA (4 mg every 6 months) in premenopausal, ER-positive breast cancer patients receiving endocrine therapy. This study recently reported an improvement in disease-free survival, in addition to favorable effects on BMD.[38] ABCSG-12 provides additional support for the metastasis-suppressing potential of adjuvant BPs. Yet this study enrolled only a narrow subset of breast cancer patients: premenopausal women with estrogen receptor-positive tumors who did not receive adjuvant chemotherapy. Extrapolation of these findings to postmenopausal women, ER-negative tumors, and women receiving chemotherapy will require data which will be supplied by ongoing clinical trials. The Z-FAST, ZO-FAST and EZO-FAST trials enrolled postmenopausal women with ER-positive tumors receiving letrozole and randomized them to "immediate" versus "delayed" zoledronic acid therapy (4 mg every 6 months for 5 years). A recent combined analysis of these trials showed lower recurrence rates in the group receiving up-front ZA therapy.[39]

Recently closed and ongoing clinical trials will help to further elucidate the effect of BPs on recurrence of breast cancer. Two large adjuvant trials, each involving over 3000 women,

have reached their targeted accruals but are yet to report. The B-34 trial of women with stages I and II breast cancer closed in 2004. This study compared 3 years of oral clodronate to placebo with the primary endpoint of disease-free survival and secondary endpoints of skeletal-related events including bone metastases. The AZURE trial enrolled stages II and III breast cancer patients and compares standard cancer therapy alone versus standard cancer therapy plus ZA given monthly for 6 doses, then every 3 months for 8 doses, followed by every 6 months for 5 doses. This trial closed in 2006. The North American Breast Cancer Intergroup, in combination with the NSABP, is conducting SWOG S0307, a comparison of three bisphosphonates in the adjuvant breast cancer setting. This trial in 5500 patients compares oral clodronate (1600 mg daily) versus oral ibandronate (50 mg daily) versus ZA (4 mg iv monthly for 6 months, then every 3 months), all for 3 years duration. The results of these trials will be critical in determining how broadly applicable adjuvant BPs are across the spectrum of early stage breast cancer patients.

Other bone-targeted agents are at earlier stages of development. The RANK ligand inhibitor denosumab is the most advanced candidate being investigated in the adjuvant setting. Recent data show promise for this agent in the treatment of bone metastases as compared to ZA.[40,41] In addition to BPs and denosumab, several other new classes of agents with anti-osteoclastic activity are in earlier stages of investigation for prevention and treatment of bone metastases. Odanacatib, a highly selective inhibitor of cathepsin K activity, has been shown to reduce the level of urinary N-telopeptide (NTX) by a similar magnitude to ZA in patients with metastatic breast cancer.[42] Although the focus of development with this agent is in postmenopausal osteoporosis, further studies in cancer are planned. Several inhibitors of Src kinase activity are being considered. In addition to possible direct effects on the cancer, these agents are potent inhibitors of osteoclast activity and may have a specific role in the future for the treatment or prevention of bone metastases.[43]

Priorities for future research

The following clinical and research priorities are proposed to address critical gaps in the development of bone-targeted agents for metastasis prevention:

- Assess bone-targeted therapies in combination with radioisotopes and/or chemotherapy.
- Determine whether the benefit of adjuvant ZA is limited to hormonal therapy or is also seen in patients receiving adjuvant chemotherapy. Is the benefit seen only in patients with accelerated bone turnover which may create a more favorable environment for tumor cell growth?
- Identify and develop biomarkers to assist in selecting those patients more likely to benefit from bone-targeted therapies.
- Study adjuvant ZA and denosumab in other solid tumors to determine whether they can play a role in preventing disease relapse beyond breast cancer.
- Determine optimal doses of ZA for metastasis prevention.
- Assess appropriate primary endpoints for future studies of adjuvant bone-targeted therapies. If the primary effect of these agents is via the bone, then bone metastasis-free survival may be more sensitive. If some agents have a direct anti-tumor effect or synergy with chemotherapy, disease-free survival may be more meaningful. If agents are expected to be widely used over long periods of time, overall survival may be most appropriate.
- Assess novel surrogates of efficacy for future trials. Consider skeletal imaging using PET, MRI or other modalities to measure changes.

Management strategies to prevent cancer therapy-induced bone loss

Breast cancer

Aromatase Inhibitors (AIs) have become the standard of care for the endocrine treatment of breast cancer in postmenopausal women. All AIs are associated with loss of bone density and concomitant increased risk of fracture in unselected populations.[44] The necessity to address accelerated bone loss in these at-risk populations is highlighted by studies showing the negative impact of fractures on patient independence and quality of life.[45] Therefore, reducing the associated costs of treatment and maintaining functional independence and quality of life during long-term adjuvant hormone blockade treatment is a principal objective of treatment. Recent evidence also suggests that up to 60% of women beginning AI therapy after 5 years of tamoxifen already have osteopenia or osteoporosis.[46]

The Z-/ZO-/E-ZO-FAST trials have convincingly demonstrated that ZA (4 mg every 6 months) administered concomitantly with an AI can prevent CTIBL and even increase BMD in patients who would otherwise experience bone loss.[47–49] Furthermore, ZA (4 mg every 6 months) has demonstrated efficacy for preventing bone loss in premenopausal women receiving tamoxifen or anastrozole after goserelin-induced menopause.[50] Other agents also appear to preserve BMD in postmenopausal women receiving AIs. In small randomized clinical trials, risedronate,[51] ibandronate,[52] and denosumab[53] have all been shown to improve BMD.

A recent health economic analysis of the Z-FAST trial, based on practice and costs within the United Kingdom, demonstrated that ZA is cost effective in preventing fractures in women with early breast cancer receiving AI therapy,[54] particularly when treatment is initiated before bone loss occurs. However, the conclusions were limited by the lack of fracture data from Z-FAST. To enable oncologists to identify patients who will benefit the most from up-front BP therapy and support treatment decisions, practice guidelines should incorporate risk factors in addition to BMD that are known to modify fracture risk.[55]

Prostate cancer

Androgen deprivation therapy (ADT), the mainstay of treatment for locally advanced, recurrent, and metastatic prostate cancer accelerates bone turnover and decreases BMD. Like AI therapy for breast cancer, ADT is associated with greater risk for clinical fractures.[56] While many clinicians now recognize the importance of treatment-related osteoporosis in prostate cancer, there is a variety of challenges that limit the routine use of adjuvant bone-targeted therapy in prostate cancer survivors.

To date, most studies have evaluated the effects of bone-targeted therapies on bone mineral density rather than fractures. Several small randomized controlled trials have demonstrated that bisphosphonates including pamidronate,[57] ZA,[58] and alendronate[59] increase BMD and decrease markers of bone metabolism in men on ADT. Other small randomized controlled trials have demonstrate that the selective estrogen receptor modulators raloxifene and toremifene also increase bone mineral density and decrease markers of bone metabolism in men treated with ADT. However, adoption as routine therapy is limited by lack of fracture prevention data.

Preliminary results from a recent international phase III study of toremifene versus placebo powered to demonstrate fracture prevention showed that toremifene significantly decreased new vertebral fractures and increased BMD at all measured skeletal sites.[60] In a phase III study of denosumab versus placebo in men receiving ADT, denosumab reduced the 3-year incidence of new vertebral fractures, fractures at any site, and multiple fractures at any site.[61] Unlike BP use, there is a significant rebound osteoclastogenesis after stopping denosumab

that results in post treatment accelerated bone loss. The clinical relevance of this is unclear and awaits further study.

Assessment of relative benefits and harms for the individual patient represents another key challenge in the use of adjuvant bone-targeted therapy to prevent fractures. Although the studies discussed above provide a high level of evidence about efficacy and safety in well-defined patient populations, they were not designed to provide guidance about optimal patient selection for drug therapy. Currently there are no evidence-based guidelines to select men with prostate cancer for drug therapy to prevent fractures, though some investigators and organizations have recommended use of National Osteoporosis Foundation (NOF) guidelines developed for the general population.

Priorities for future research and education

To address critical knowledge gaps and clinical care needs related to prevention cancer therapy-induced bone loss, the following priorities for research and education and proposed:

- Assess impact of adjuvant therapies on fracture risk, not just BMD. While prostate cancer studies have shown evidence that adjuvant therapy can affect fracture rates, in breast cancer there is no direct evidence that fracture rates are affected.
- Determine whether lower doses of ZA or alternative schedules of bisphosphonates are appropriate for bone loss prevention associated with cancer therapies with a view to reducing side effects, cost and duration of therapies.
- Assess mechanisms of rebound osteoclastogenesis with denosumab and its clinical relevance in the oncology setting.
- Focus physician education on complications of fracture risk associated with hormone deprivation and steroids.
- Validate guidelines for bone loss associated with cancer therapies. International guidance including BMD and BMD independent risk factors for fractures have been recently introduced into clinical practice but have not yet been validated in clinical studies.
- Update and validate FRAX (www.shef.ac.uk/FRAX/) model for use in cancer patients. Include data from recent studies on cancer therapy-induced bone loss (CTIBL).
- Evaluate if measurement of markers of bone turnover can be applied to identify the population at highest risk, as well as the optimal dose, schedule and duration of treatment.
- Determine whether reduced serum levels of vitamin D and and/or insufficient intake of calcium significantly contributes to CTIBL and the impact of supplementation has on the effects of bisphosphonates or denosumab.
- Develop reliable assessments of bone quality. Measurement of BMD only evaluates one dimension of the problem. Novel imaging, such as quantitative (Extreme) CT, novel spiral CT technology, MRT or quantitative ultrasound of bone may provide useful information to assess parameters of bone quality. Bone biopsies provide the ultimate information but a combination of the invasive nature of the procedure, shortage of trained personnel to take bone biopsies or to provide the specialist histomorphometric reports limits their utility, especially in the oncology setting.

Conclusion

Prevention of bone metastasis and bone loss are at the intersection of multiple avenues of basic and clinical research and exciting new insights into tumor and bone biology and pathogenesis. Table 1 summarizes recommended priorities to advance understanding of bone metastasis, critically evaluate bone-targeted therapies to prevent metastasis and bone loss, and advance physician education.

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Table 1

Summary of recommendations.

Pathophysiology and preclinical research
• Continue to investigate the role of the many components of the bone microenvironment and their effects on tumor growth
• Further study the effects of bone-targeted therapies on bone, tumor and immune cells, in vitro, in vivo and in human samples
• Utilize preclinical models to study combination therapies targeting both the tumor and bone microenvironment to optimize the anti-tumor effect
Clinical research
• Assess bone-targeted therapies with radiation and with chemotherapy
• Assess novel bone-targeted therapies in solid tumors, especially anabolic agents
• Optimize dose and schedule of ZA and denosumab for indications beyond osteoporosis
• Develop biomarkers to assist in patient selection for adjuvant therapies
• Determine optimal endpoints for future clinical studies of adjuvant bone-targeted agents and assess whether new bone imaging modalities can play a useful role
Physician education
• Educate physicians on long-term consequences of fracture risk associated with cancer therapies and steroids
• Validate treatment guidelines for CTIBL