

## Advancing Treatment for Metastatic Bone Cancer: Consensus Recommendations from the Second Cambridge Conference

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**Abstract Purpose:** Summarize current knowledge, critical gaps in knowledge, and recommendations to advance the field of metastatic bone cancer.

**Experimental Design:** A multidisciplinary consensus conference was convened to review recent progress in basic and clinical research, assess critical gaps in current knowledge, and prioritize recommendations to advance research in the next 5 years. The program addressed three principal topics: biology of metastasis, preserving normal bone health, and optimizing bone-targeted therapies.

**Results:** A variety of specific recommendations were identified as important to advance research and clinical care over the next 5 years.

**Conclusions:** Priorities for research in bone biology include characterizing components of the stem cell niche in bone, developing oncogenic immunocompetent animal models of bone metastasis, and investigating the unique contribution of the bone microenvironment to tumor growth and dormancy. Priorities for research in preserving normal bone health include developing methods to measure and characterize disseminating tumor cells, assessing outcomes from the major prevention trials currently in progress, and improving methodologies to assess risks and benefits of treatment. Priorities for optimizing bone-targeted therapies include advancing studies of serum proteomics and genomics to reliably identify patients who will develop bone metastases, enhancing imaging for early detection of bone metastases and early response evaluation, and developing new tests to evaluate response to bone-directed treatments.

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 (1). At present, once cancer metastasizes to bone, it is incurable and can cause severe morbidity and mortality. Bone metastases are often associated with skeletal-related events (SRE), which include severe pain, bone fractures, need for radiation therapy to bone, need for surgery to bone, spinal cord compression,

and bone demineralization. Bisphosphonate therapy, the current standard of care for metastatic bone cancer, has been shown to decrease the risk of SREs by up to 50% and slow the rate of development of SREs (2). Although this therapeutic advance is of major clinical significance, bisphosphonate therapy does not completely block bone metastasis. In addition, bisphosphonate therapy is occasionally associated with renal toxicity and osteonecrosis of the jaw. Thus, new strategies are needed to develop bone-targeted agents to both

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## Translational Relevance

The skeleton is both the most common organ affected by metastatic cancer and the site that produces the greatest morbidity for patients. Recent advances in our understanding of bone biology and the pathways by which cancer metastasizes and spread to bone have contributed to the development of several important new drugs targeting these processes, and focused research on further understanding the biology and targets involved in metastasis and bone loss. This article summarizes our current knowledge, critical gaps, and recommendations to advance the field over the next 5 years in three aspects of the field: the biology of metastasis, predicting who is at risk for skeletal-related events, and recent advances in clinical research in bone-targeted therapies. This information is relevant for both clinicians who assess, counsel, and treat patients at risk for metastatic complications and those involved in basic and translational research in bone and cancer biology.

prevent the development of bone metastases, as well as to effectively treat metastases and their complications when they occur. This multidisciplinary consensus conference was convened to review recent progress in basic and clinical research, assess critical gaps in current knowledge, and prioritize recommendations to advance research in the next 5 years. Three principal areas of investigation addressed were as follows: (a) biology of metastasis with a focus on stem cell interactions with bone, initiators, and mediators of metastasis and the effects of bone targeted therapies on the bone microenvironment; (b) preserving normal bone health, with a focus on predicting who will develop bone metastases and the role of adjuvant bone-targeted therapies to prevent metastasis and bone loss; (c) optimizing bone-targeted therapies, with a focus on assessing risk and response, approaches to personalized treatment and new treatments, and combination strategies.

## Biology of bone metastasis

The principal focus of research on the biology of bone metastasis is on understanding and identifying stem cell interactions with the stem cell niche in the bone marrow, initiators and mediators of metastasis, and the effects of bone-targeted therapies on the microenvironment in cancer cells.

### Stem cell niche

The concept of a stem cell niche has been proposed for many decades because of initial observations that hematopoietic stem cells are found in very discrete areas in the bone marrow. Bone marrow stromal cells derived from mesenchymal stem cells are believed to provide the cellular basis for the physical structure of the niche. The stem cell niche is thought to regulate hematopoietic stem cell renewal, proliferation, and differentiation through production of cytokines and cellular signals that are initiated by cell-to-cell adhesive interactions between hematopoietic stem cells and the components of the stem cell niche. Recent studies have shown that osteoblasts comprise a crucial component of the

hematopoietic stem cell niche, "the endosteal niche," and cells of other lineage, including endothelial cells, probably participate in these stem cell functions (3). Although much has been learned recently about the identity and role played by the cytokines and adhesive molecules involved in the niche interactions between stem cells and osteoblasts, it is still unclear what subpopulation(s) of osteoblasts actually comprise the niche and how these cells interact with other cell types within the marrow microenvironment to form the niche and regulate hematopoietic stem cell quiescence, proliferation, and differentiation (4).

Recent studies have shown that annexin II, in addition to SDF-1, is produced by osteoblasts and plays an important role in the adhesion of hematopoietic stem cells to the endosteal niche (5). Hematopoietic stem cells express the annexin II receptor as well as CXCR4, which bind annexin II and SDF-1, respectively, that enable homing of hematopoietic stem cells to the niche. Similarly, prostate cancer cells express both these molecules and seem to also use the stem cell niche for homing to the bone marrow. However, it is unclear if cancer cells use the same niche as hematopoietic stem cells, and whether, as preliminary studies suggest, cancer cells can displace hematopoietic stem cells from the niche and supplant them (6).

Among the many important questions that need to be addressed are as follows: (a) what subsets of osteoblasts comprise the endosteal niche; (b) how do these cells interact with other cell types including endothelial cells that are involved in the vascular niche; (c) whether cancer cells actually bind within the same niche as hematopoietic stem cells and whether they displace hematopoietic stem cells; and most importantly, because little, if anything, is known about the human stem cell niche, (d) what are its characteristics? Furthermore, methods are needed to visualize the stem cell niche and to track cancer cells and hematopoietic stem cells as they interact with the niche. An additional important area of future investigation includes understanding how cancer cells affect hematopoietic stem cells and how both of these cell types affect cells in the niche.

### Initiators and mediators of metastasis

Much research on mechanisms responsible for bone metastasis has focused on the regulation of osteoclastic bone resorption and bone formation in xenograft models. It has become abundantly clear however that tumor xenograft models in immunocompromised animals, although instructive, are not completely accurate models for the tumor phenotype in bone or the effects of tumors on the bone microenvironment. An important research need is the development of bone metastasis models that are generated and maintained in immunocompetent animals. This type of model would be much more appropriate to assess the interactions between osteoclasts, osteoblasts, and other cell types in the bone marrow microenvironment and how they interact with tumor cells. Furthermore, understanding the role of changes in the bone vasculature induced by tumors is an important area that needs to be further explored. The influences of the lack of an immune system in most xenograft models, as well as the strain-specific differences of inbred mouse strains, their effects on the growth of tumor cells, and their interactions with the marrow microenvironment need to be better defined.

### Myeloma bone disease

There is ongoing controversy as to what is the tumor-initiating cell in myeloma, with investigators suggesting that it is a memory B cell, whereas others suggest it is the malignant plasma cell itself that propagates the tumor. Although many of the cytokines induced by myeloma cells in the bone microenvironment that stimulate osteoclast formation and suppress osteoblast activity have been identified, we need to better understand how these factors are regulated and why myeloma cells respond differently to signals within the bone marrow microenvironment as opposed to outside this environment. Recent studies by Edwards and coworkers (7) have shown that stimulating WNT signaling in the bone microenvironment suppresses the growth of myeloma cells, whereas stimulating WNT signaling outside the bone marrow microenvironment enhances the growth of myeloma cells. The basis for these differences is currently unknown and is an important area of investigation. Furthermore, the question of whether the "vicious cycle," which has been clearly identified in murine systems, can be used as a way to target tumor growth in patients is still an open question. Preclinical studies in animal models have shown that blocking bone resorption decreases tumor burden but this has not been clearly shown in patients (8). It is unknown if this is a function of the differences between patients and the models used, or whether there is insufficient suppression of bone resorption in patients to affect tumor burden. Other important areas of research are the development of better imaging techniques to quantitate tumor burden in bone and evaluation of the role of angiogenesis in tumor progression. Finally, the contribution of other cell types, such as platelets and hematopoietic cells to the bone metastatic process, is an important area for further investigation.

### Therapeutic targets in bone cancer

Transforming growth factor  $\beta$  (TGF- $\beta$ ) is a major therapeutic target for osteolytic bone metastasis due to breast cancer and other solid tumors, including prostate cancer and melanomas. Studies in animal models have shown that TGF- $\beta$  signaling directly inhibits production of osteolytic and prometastatic factors and also increases bone mass, independent of its effects on cancer cells, by increasing osteoblast activity and decreasing osteoclast activity. Recently, the effects of TGF- $\beta$  have been shown to be potentiated by zoledronic acid (9). Another important observation is that other cancer therapies seem to have adverse effects on bone. The anticancer drug 17AAG increases osteoclast activity in bone metastasis in mice, although it has been used as a potential therapeutic agent in treating tumors (10). Furthermore, loss of CXCR4 on bone cells causes low bone mass and increases osteoclast activity (11). These findings suggest that targeted therapies for cancer and bone metastases may have differential effects on bone, depending on the tumor phenotype and effects of the targeted therapy on normal bone remodeling. Important issues that need to be addressed in the future include how to prioritize which bone-targeted therapies identified in preclinical studies should be pursued clinically; how bone cells affect each other; and in particular, how bone-targeted therapies affect normal and neoplastic bone remodeling. Importantly, there is a great need to assess the activity of combination therapies such as TGF- $\beta$  antago-

nists with bisphosphonates or other agents to treat bone metastasis. These studies have only just begun.

### Bone cell interactions

Bone cell interactions are clearly important in regulating both normal bone formation as well as osteoclast-mediated bone resorption. It has long been recognized that osteoblastic cells regulate osteoclast formation, activity, and survival through their expression of macrophage-colony stimulating factor and receptor activator of nuclear factor  $\kappa$  B ligand in response to numerous influences, including cytokines and growth factors released by inflammatory and malignant cells (12). It has also been known for several years that osteoclasts and osteoclast progenitors produce cytokines in response to many of these influences, but until recently, the effects of these osteoclast-produced cytokines were unknown.

Recent studies have reported cytokines, such as tumor necrosis factor and interleukin-1, secreted by osteoclasts and their precursors regulate their own formation and activity (13). Furthermore, osteoclasts influence the egression of hematopoietic progenitors and stem cells from their niche in the bone marrow into the peripheral blood (14). It is not known if they also are involved in the homing of these cells back into niches in the marrow, but if they are, they could potentially also regulate the egression of circulating tumor cells from the blood into the marrow. Interactions between osteoclast and osteoblast precursors in the marrow not only induce osteoclast differentiation but may also inhibit the differentiation of these cells by so-called reverse signaling through the ligand, Ephrin B2, on the surface of osteoclast precursors (15). More surprisingly, forward signaling through the Eph 4 receptor promotes the differentiation and activity of osteoblasts. Osteoclasts can also negatively regulate the differentiation of osteoblast precursors through secretion of a soluble factor (16). Thus, they could contribute to the inhibition of bone formation that occurs in osteolytic bone metastases.

The effects of autocrine-paracrine factors produced by osteoclasts on other cells in the bone marrow microenvironment are just beginning to be appreciated and are an important area of study. In particular, osteoclasts produce vascular endothelial growth factors, which can affect lymphoangiogenesis around inflamed joints of mice with inflammatory arthritis (17). Whereas inhibition of osteoclast activity limits tumor growth in bone, complete inhibition of osteoclast functions could adversely affect osteoblastic filling of lytic lesions. In addition, it is possible that inhibition of vascular endothelial growth factor expression by osteoclastic cells might adversely affect immune responses in inflammatory arthritis by preventing the development of lymphatic vessels and the removal of noxious agents from the joints. Modulation of the effects of bone cells on other cell types and their interactions with the bone microenvironment are important areas that need further study and should be major targets of research on bone metastasis.

### Bone biology: research priorities

Based on our review of recent progress and our assessment of where a focus of resources would be expected to contribute most to this field in the next 5 years, several research priorities were identified (see Table 1). These include the following: (a) characterizing cellular components involved in the stem cell

**Table 1.** Research priorities next 5 years**Bone biology**

- Characterize components of the stem cell niche in bone
- Develop oncogenic immunocompetent animal models of bone metastasis
- Investigate the unique contribution of the bone microenvironment to tumor growth and dormancy
- Investigate how bone-targeted therapies affect normal bone remodeling
- Investigate combination therapies for bone metastasis
- Investigate effects of bone cell interactions on osteoclast and osteoblast activity and their effect on tumor growth in bone

**Preserving normal bone health**

- Assess outcomes from major ongoing prevention trials, i.e., appropriate use of bisphosphonates and the optimum duration of therapy
- Improve methodologies to assess risks and benefits of treatment
- Improve clinical methodologies to assess risk of bone loss and fracture, when to intervene, optimum dose, and schedule of treatment
- Validate the recently introduced AIBL guidance

**Optimizing bone-targeted therapies**

- Develop methods to measure and characterize DTCs, with a focus on dormancy and changes in response to therapy
- Advance studies of serum proteomics and genomics to reliably identify patients who will develop bone metastases
- Enhance imaging for early detection of bone metastases and early response evaluation
- Develop new tests to evaluate response to bone-directed treatments
- Investigate sequence of administration of chemotherapy and zoledronic acid for antitumor response
- Advance clinical studies of new bone-directed therapies such as Denosumab
- Advance clinical studies of cathepsin-K inhibitors and src inhibitors
- Study combinations of bone-directed therapies—e.g., osteoclast + osteoblast inhibitor in osteolytic disease
- Explore use of agents to prevent bone metastases in large prospective randomized trials
- Develop alternative trial designs/end points to shorten trial duration and decrease size

niche and how it functions to maintain normal and malignant stem cells and progenitors; (b) developing oncogenic immunocompetent animal models of bone metastasis that more accurately reflect the clinical situation; (c) investigating the unique contribution of the bone microenvironment to tumor growth and dormancy compared with other tissue microenvironments; (d) investigating how bone-targeted therapies for metastasis affect normal bone remodeling; (e) investigating combination therapies for bone metastasis; and (f) investigating the effects of bone cell interactions on osteoclast and osteoblast activity and their effect on tumor growth in bone.

**Preserving Normal Bone Health****Predicting who will develop bone metastases**

Other than the use of standard clinical and pathologic risk factors in breast cancer and prostate specific antigen kinetics in prostate cancer, the prediction of who is most likely to develop

bone metastases remains very difficult (18). Measurement of cell surface receptors and protein expression (19) and genetic profiling of the primary tumor may be informative, but conference participants were not optimistic that such approaches would provide clinically useful information in the next 5 years. More reliable prediction will require study of the target organ for metastasis rather than the primary lesion, as well as a better understanding of the bone microenvironment and the interactions between tumor cells, bone cells, and marrow stromal cells.

**Risk assessment for metastasis**

In patients with breast cancer, estrogen-receptor status was associated with the development of metastasis to bone (20). Patients with prostate cancer and a markedly elevated prostate-specific antigen (>10 ng/mL) or high prostate-specific antigen velocity are also more likely to develop bone metastases. In a study of patients with non-small cell lung cancer, a panel of 10 biochemical markers was evaluated in tumor samples from patients with bone metastases, without metastases, and with visceral metastases only. In this panel, only bone sialoprotein significantly correlated with the presence of bone metastases (21).

Clearly, more work is needed to develop sensitive and reliable predictors for the future development of bone metastases. For example, data from genetic profiling studies of primary tumor samples from patients with breast cancer have revealed specific genes that are differentially expressed in samples from patients whose cancer recurred in bone versus patients whose tumor relapsed in viscera (22). A 31-gene profile classifier was developed by this group that may be a useful tool for predicting the risk of bone metastases in breast cancer patients. Further work is required to more reliably identify the patients at high risk for bone metastases who could benefit from bisphosphonates or other potentially useful bone-targeted therapy in the adjuvant setting.

Preclinical and emerging clinical data indicate that bisphosphonates may prevent the development of skeletal metastases in patients with cancer. Clodronate has shown efficacy in this setting, although results from initial studies have been inconsistent (23). In a pilot study of patients with solid tumors, zoledronic acid significantly prolonged bone metastasis-free survival (24). Most recently, zoledronic acid decreased the incidence of metastatic disease in premenopausal patients receiving adjuvant treatment with goserelin plus either tamoxifen or an aromatase inhibitor (25).

Large prospective clinical trials are currently ongoing to confirm the potential use of bisphosphonates in the prevention of bone metastases in a variety of malignancies. Knowing which patients are most likely to develop bone metastases would allow for treatment of a more specific high-risk population of patients. Others would be spared the inconvenience and potential toxicity of adjuvant bisphosphonate therapy, whereas the economic burden to health care budgets would become more manageable.

**Use of disseminated and circulating tumor cells**

The study of circulating and disseminating tumor cells (DTC) is revealing a great deal about the metastatic process. It is abundantly clear that these cells begin to disseminate early in the disease process and can survive at distant sites such as the bone marrow for long periods, sometimes in excess of 10 years.

The number of circulating tumor cells and DTCs detected is highly variable, ranging from an occasional cell in some patients at initial presentation to sometimes thousands in patients with advanced disease.

Depending upon the cancer type and the method used for detection, the frequency of detecting cancer cells in the blood or bone marrow of patients upon initial presentation ranges widely, from ~20% to 80%. Patient groups with higher stage disease have a higher number of carcinoma cells detected in their bone marrows than those with lower stage disease. In breast cancer, immunocytochemical detection of DTC in the bone marrow of patients with primary breast cancer is associated with an increased risk of recurrence as well as cancer related death (26). In prostate cancer, correlations between detection of DTC and subsequent biochemical recurrence, metastases to bone, and overall survival have been mixed (27). DTC detection in the preradical prostatectomy setting seems to be less predictive than in the follow-up of patients following radical prostatectomy in biochemical (prostate-specific antigen) remission (28).

The effects of treatment on DTC have been less studied. In breast cancer, chemotherapy has been shown to decrease the number of bone marrow DTC detected. In metastatic breast cancer, a reduction in circulating tumor cells in response to treatment is associated with an improved outcome (29).

Important knowledge gaps in this area of investigation include the following: understanding the genetic nature of DTC and how they differ from primary breast tumor cells; determining whether DTC cycle or are dormant; assessing whether the presence of DTC reliably predict who will develop bone metastases; determining whether DTC in the bone marrow are a reservoir of cancer cells that eventually metastasize elsewhere; and assessing whether changes in the bone microenvironment alter DTC growth and dissemination. To make progress in understanding the clinical relevance of circulating tumor cells and DTCs, we need to advance the technologies to accurately study and characterize single cells or small numbers of cells and develop model systems that reflect the clinical phases of dissemination as well as tumor cell dormancy. Of course, one of the critical questions is what triggers dormant tumor cells to become active? Additionally, in both breast and prostate cancer settings, multiple cell detection methodologies have been used and there is an urgent need for a standardized, reproducible methodology to advance the technology.

#### **Role of adjuvant bone-targeted therapies to prevent metastasis and bone loss**

There are copious data to show that increased osteoclastic bone resorption is associated with progression of bone disease in patients with skeletal metastases (30). The synergy between increased bone resorption and tumor progression is further illuminated by the ability of inhibitors of bone resorption to reduce the incidence of skeletal complications in advanced disease. Animal models also provide consistent data supporting a direct relationship between increased bone turnover and the early development of bone metastases. In such models, bisphosphonate therapy is usually associated with decreased osteolysis and bone marrow tumor burden. These observations have been mirrored by several studies in early breast cancer initially with daily oral clodronate and more recently with

zoledronic acid (23, 25). Confirmation of the utility of bisphosphonates in this setting awaits results from two ongoing studies: (a) the Adjuvant Zoledronic acid to Reduce Recurrence trial, which has finished accrual of 3,360 relatively high-risk patients with stage II or III breast cancer, and (b) the National Surgical Adjuvant Breast and Bowel Project B-34 trial of adjuvant clodronate, which has randomized over 3,000 women with stage I to III breast cancer (31).

Given that one or more of these studies is likely to be positive, several important issues remain to be addressed and should be the focus of future developments. These include the need for bone protection from aromatase inhibitor-induced bone loss (AIBL), specifically addressing whether the aim of treatment is to prevent bone loss (low metastatic risk), metastases (high metastatic risk), or both in an individual patient. Additionally, assessing appropriate dose and duration of therapy, and determining whether further benefit is to be gained by using even more potent inhibition of osteoclast activity with, for example, antibodies to receptor activator of nuclear factor  $\kappa$  B ligand, i.e., Denosumab, will be important (32). It will also be important to determine whether the effects are organ specific or disease specific; in other words, will similar beneficial effects be seen only in breast cancer, or in prostate and other cancers with a propensity for metastasis to bone?

The effects of bone-targeted therapy on visceral metastases are also of interest. Several studies suggest that extraskeletal disease is favorably affected by these therapies. Thus, it is important to determine whether this is a direct effect or mediated by either reduced tumor growth in bone (reduction in secondary metastasis) and/or disruption of migration of bone marrow-derived cells to the premetastatic niche. Additionally, it is important to determine whether changes in metastatic behavior are due to stimulation of bone formation or perhaps, more specifically, the removal inhibitors of bone formation (33).

In parallel to mechanistic questions, clinical questions remain with regard to targeting and monitoring bone therapies in the setting of metastasis prevention. If treatments are safe and cheap, which is unlikely in the near future, should they be administered to all? Conversely, if therapies are only beneficial to some patients, can we improve on predictors of skeletal metastases over the currently used clinical staging by either further evaluation of the primary tumor, detection, and characterization of DTC and/or measurement of bone derived markers?

#### **Management of treatment-induced bone loss**

Recent studies indicate that women with breast cancer are at increased risk of fracture compared with their age-matched peers. Current American Society of Clinical Oncology guidelines on bone health issues in women with breast cancer recommend that women with osteoporosis (T-score, <-2.5) receive bisphosphonate therapy to increase bone mineral density (BMD) and reduce the risk of fracture, and osteopenic women (T-score, -1 to -2.5) receive therapy on an individualized basis (34). Because the majority of fractures occur in osteopenic women, this threshold seems inadequate for averting fractures in patients with breast cancer, particularly those receiving aromatase inhibitor therapy. BMD measurement should not be the sole criterion to assess fracture risk, and therefore, there is a need to identify clinically relevant

predictors for fracture that can be used to assess overall fracture risk, as exists for fracture prediction in postmenopausal women, and to provide practical guidance for preventing and treating bone loss in women with early breast cancer. A number of algorithms have recently been formulated and there is a need to validate their clinical utility (35).

Recently, a specific guidance for the prevention and treatment of AIBL was introduced by an international expert group. This evidence-based approach was conducted in accordance to the American Society of Clinical Oncology guidelines and included BMD as well as relevant risk factors for fracture, which independent of BMD, substantially contributes to fracture risk (35). Additionally, AIBL-specific prevention and treatment recommendation were included based on the published studies.

The WHO has recently developed a new fracture risk assessment tool, called FRAX, to identify individuals at high risk of osteoporotic fracture. This new tool uses clinical risk factors with femoral neck BMD or body mass index, if BMD is not available, to determine the patient's 10-year probability of hip fracture and the 10-year probability of major osteoporotic fracture (clinical vertebral, forearm, hip, and shoulder). However, it does not relate to cancer induced bone loss or AIBL and does not identify the level of fracture risk at which treatment should be started. FRAX is currently being validated in additional longitudinal cohort databases and is available to clinicians online at the FRAX Web site (36).<sup>16</sup>

Randomized clinical trials indicate that bisphosphonates prevent treatment induced bone loss in both breast cancer and prostate cancer patients on endocrine therapy (37, 38). Most data exists with zoledronic acid 4 mg every 6 months, but there is a need to confirm whether this is the optimum agent and schedule of treatment.

#### Preserving normal bone health: research priorities

Based on our review of recent progress and our assessment of where a focus of resources would be expected to contribute most to this area of research in the next 5 years, several priorities were identified (see Table 1). These include the following: (a) assessing the outcomes from the major prevention trials currently in progress to address appropriate use of bisphosphonates, whether we are overtreating, and the optimum duration of therapy; (b) improving methodologies to clinically assess risks and benefits of treatment; (c) improving approaches to assess risk of bone loss and fracture, when to intervene, optimum dose, and schedule of treatment; and (d) validating the recently introduced AIBL guidance.

### Optimizing Bone-Targeted Therapies

#### Assessing risk and response in patient with malignant bone disease

Approximately half of all patients with bone metastases develop SREs. The development of SREs as well as the number and size have been shown to be related to a significant decrease in overall survival (39). Bisphosphonates are an effective tool for reducing the incidence and delaying the onset of SREs. In patients with solid tumors, multiple factors including a prior

SRE, the presence of more than three bone lesions, bone pain, and elevated levels of markers of bone resorption are all risk factors for SREs (40). Elevated bone markers despite bisphosphonate therapy are also associated with greater risk for adverse clinical outcomes including death. These observations suggest opportunities to identify patients who require more intensive therapy as well as subsets of patients who may be managed with lower doses and/or less frequent schedules of bone-targeted treatment. Ongoing trials such as the BISMARCK trial are comparing the use of a bone marker, N-telopeptide of type I collagen, directed schedule of treatment with standard 3 to 4 weekly schedule of zoledronic acid. We must move away from the "one size fits all" treatment paradigm, and the results of this trial could usher in an era of "personalized" individually targeted therapy.

#### Personalized cancer treatment

In recent years, it has become clear that breast cancer is not one disease, but a heterogeneous collection of distinct entities that are molecularly quite different. As a result, treatments are now increasingly selected on the basis of biological rather than morphometric or clinical characteristics. In the context of metastatic bone disease, the principles are the same, with an increasingly targeted approach to therapy and individualization of therapy. Elevated baseline markers of bone resorption and bone formation are associated with a greater risk for skeletal complications and death, suggesting that risk stratification may be an effective strategy to identify patients most likely to require bone-targeted therapy. Recent studies have defined a population of patients with accelerated bone resorption in whom the use of zoledronic acid does seem to significantly improve overall survival (41).

#### New approaches to treating metastatic solid tumors

Potentially useful new compounds for the management of tumor-induced osteolysis can be classified as inhibitors of bone resorption or stimulators of bone formation.

#### Inhibiting bone resorption

**Chemotherapy and bisphosphonates.** Although the potential antitumor effects of bisphosphonates are generally believed to be secondary to the marked inhibition of bone resorption, sequential administration of chemotherapeutic drugs, such as doxorubicin, followed by bisphosphonates, such as zoledronic acid, has been shown to increase tumor cell apoptosis *in vitro*. Recently reported data in an animal model of tumor-induced osteolysis indicate that the same sequential treatment reduces intraosseous tumor growth to a greater extent than either drug alone or simultaneous treatment (42). On the other hand, daily or weekly therapy with clinically relevant doses of zoledronic acid has been shown to inhibit skeletal tumor growth in a mouse model much more efficiently than a single large dose. The same total cumulative dose of zoledronic acid was given to each mouse regardless of the dosing regimen (43). The clinical relevance of these animal observations deserves to be investigated.

**Denosumab.** An excessive production of receptor activator of nuclear factor  $\kappa$  B ligand by osteoblasts plays a key role in the pathogenesis of tumor-induced osteolysis. Denosumab, an investigational, fully human monoclonal antibody, has been shown to bind specifically to receptor activator of nuclear factor  $\kappa$  B ligand, thereby inhibiting osteoclast-mediated bone destruction and blocking the vicious cycle typical of

<sup>16</sup> <http://www.shef.ac.uk/FRAX/>

cancer-mediated bone disease (44). In a phase 2 study of bisphosphonate-naïve breast cancer patients with bone metastases, denosumab suppressed levels of bone turnover markers to an extent similar to that seen with i.v. bisphosphonates. Denosumab use was well-tolerated and associated with a low rate of SREs (32). This trend for a lower rate of SREs in denosumab-treated patients needs to be confirmed. Phase 3 head-to-head studies are ongoing to compare denosumab with zoledronic acid across the range of solid tumors and multiple myeloma. Results of these phase 3 trials, at least in breast cancer, will be available in the near future. These studies should answer the key question of whether denosumab has greater efficacy than bisphosphonates on lowering the incidence of SREs.

In another phase 2 study including “biochemically resistant” patients receiving bisphosphonate therapy, an interim analysis indicates that denosumab can normalize bone resorption much more effectively than the continuation of bisphosphonates in these patients (45). From these phase 2 trials, it also seems that treatment effects of denosumab are not affected by previous bisphosphonate exposure. This is an important point that needs to be confirmed. Although there are no clinical data on the effects of combination therapy with denosumab and bisphosphonates, the effects of denosumab on bone resorption would argue against such a trial. Lastly, studies are also planned, or in progress, to evaluate the use of denosumab for the prevention of bone metastases. The safety of investigational compounds is especially important in the adjuvant setting. However, the long-term safety of denosumab is unknown and this is probably the most important gap regarding this extremely potent and convenient inhibitor of bone resorption.

**Inhibitors of bone resorption in early clinical development.** Other potentially useful inhibitors of bone resorption include cathepsin K inhibitors, src inhibitors, integrin inhibitors, chloride channel inhibitors, and PTHrP antibodies. Cathepsin K is a lysosomal protease that is highly expressed in osteoclasts and plays a critical role in the degradation of bone collagen. Cathepsin K inhibitors have been shown in preclinical studies to reverse ovariectomy-induced bone loss and bone strength (46). Odanacatib is a highly selective cathepsin K inhibitor that has already been tested in postmenopausal women with low BMD. Eighteen months of treatment resulted in dose-related increases in BMD versus baseline at trabecular and cortical bone sites. The safety profile of 50 mg given weekly seems to be excellent and the antifracture efficacy of odanacatib is currently being tested in a phase 3 trial. Another cathepsin K inhibitor, balicatib, has already been shown to reduce breast cancer-induced osteolysis and skeletal tumor burden in an animal model. The efficacy of these cathepsin K inhibitors should be tested in cancer patients, initially in patients with tumor bone disease. Cathepsin K inhibitors do not lead to osteoclast apoptosis. Thus, the osteoclasts that survive in patients treated with cathepsin K inhibitors could have beneficial or detrimental effects on osteoblastic and tumor cells around them in bone metastases. Combination therapy with cathepsin K inhibitors and bisphosphonates should probably be evaluated.

#### Stimulating bone formation

Bone formation is typically depressed in patients with lytic bone metastases and marked therapeutic progress will probably be achieved only when stimulators of osteoblast differentiation

and/or activity will be available in addition to osteoclast inhibitors.

**Sclerostin.** Sclerostin is specifically expressed by osteocytes and inhibits differentiation and mineralization of osteoblast-like cells *in vitro*. Sclerostin knockout mice have an increased lamellar pattern of trabecular and cortical bone as well as an increase in bone strength. In aged ovariectomized rats, administration of an antisclerostin antibody leads to a dose-dependent increase in bone mass and bone formation without an increase in osteoclast number (47). The increase in bone formation seems to essentially come from quiescent bone (modeling surfaces) and not from remodeling parts.

**TGF- $\beta$ 1 kinase inhibitors.** Blockade of TGF- $\beta$  action by a TGF- $\beta$  R1 kinase inhibitor has been shown to increase osteoblast and decrease osteoclast numbers and to lead to an increase in bone mass in animal models of tumor-induced osteolysis (48). These compounds could reverse TGF- $\beta$  blockade of osteoblast differentiation in tumor-induced osteolysis. Along the same line, blockade of activin, a member of the TGF- $\beta$  superfamily, could be another means to lead to bone anabolism. A soluble activin receptor type IIA has been shown to increase bone mass and strength in normal and ovariectomized mice, and prior bisphosphonate therapy does not seem to alter the anabolic skeletal response to this compound (49). Much work remains to be done with these various agents, but use of potent stimulators of osteoblast differentiation could be particularly useful in the treatment of tumor-induced osteolysis because inhibition of osteoblast differentiation is common at sites of osteolysis.

#### New approaches to treating myeloma bone disease

Recent studies have identified several new potential targets for treating multiple myeloma bone disease. These include tumor necrosis factor receptor-associated factor 6, which is critical to the development of osteoclasts, and the combination of the bone-seeking radiopharmaceutical 153samarium (Sm)-lexidronam with the proteasome inhibitor bortezomib. (Sm)-lexidronam has been shown to reduce bone pain for patients with metastatic bone disease, although it has not been approved as a therapeutic modality to treat any cancer. A phase I clinical trial evaluating this combination in multiple myeloma patients with progressive disease showed that it was well-tolerated and had clinical activity for patients with relapsed or refractory disease.

Monoclonal gammopathy of undetermined significance is the most common plasma cell dyscrasia involving >5% of individuals over age 70 years. These patients have a high prevalence of osteoporosis and fractures. Zoledronic acid 4 mg every 6 months has been shown to increase BMD among monoclonal gammopathy of undetermined significance patients with osteopenia or osteoporosis as determined by BMD (50).

Other inhibitors of bone loss in early clinical development for multiple myeloma bone loss include antibodies to dickkopf (DKK)-1 and inhibitors of macrophage inflammatory protein 1, which has been shown to be important in the induction of osteoclastic activity in these patients.

#### Optimizing bone-targeted therapies: research priorities

Based on our review of recent progress and our assessment of where a focus of resources could be expected to contribute most to this area of research in the next 5 years, several priorities were identified for future research to advance the treatment of bone

metastases (see Table 1). These include the following: (a) developing methods to measure and characterize DTCs, including understanding dormancy and developing methods to measure single cells (small numbers of cells) and DTC changes in response to therapy; (b) advancing studies of serum proteomics and genomics to reliably identify patients who will develop bone metastases; (c) enhancing imaging for early detection of bone metastases and early response evaluation; (d) developing new tests to evaluate response to bone-directed treatments; (e) investigating the sequence of administration of chemotherapy and zoledronic acid in terms of antitumor response; (f) studying new bone-directed therapies such as Denosumab; (g) advancing clinical studies of cathepsin-K inhibitors and src inhibitors; (h) studying combinations of bone-directed therapies such as osteoclast + osteoblast inhibitor for osteolytic disease; (i) investigating the use of agents to prevent bone metastases in large prospective randomized trials; and (j) developing alternatives to trial designs based solely on

risk for SREs to shorten the time of these studies and decrease the number of patients needed to complete these trials.

### Disclosure of Potential Conflicts of Interest

J. Berenson: Research grants/consultant/speaker, Celgene, Cephalon, Millenium and Novartis; Consultant/research grants, Amgen, CuraGen, CytoGen, Seattle Genetics; Consultant/speaker, OrthoBiotech; Research grants, Pfizer and ZymoPharm. J.J. Body: Consultant/speaker, Amgen, Novartis and Roche. R.E. Coleman: Consultant, expert witness, and speaker, Novartis; Consultant/speaker, Amgen; speaker, Hoffman LaRoche. T.A. Guise: Leadership: ASBMR, ASCI, FPJN, IBMS, and PAGEJ; Consultant/speaker, Amgen; Speaker, Merck and Novartis; Research funding, Scios. A. Lipton: Consultant/Speaker/expert testimony, Novartis; Consultant/speaker, Amgen. E.V. McCloskey: Research grant/speaker, Amgen; Research grant, Novartis; Speaker, Merck. F. Saad: Advisor: Amgen, Merck, and Novartis; Research support, Amgen and Novartis; Speaker, Novartis. G.D. Roodman: Consultant, Amgen, Novartis, Merck and Millennium; Scientific Advisory Board, International Myeloma Foundation, and Multiple Myeloma Research Foundation; Employee, University of Pittsburgh and VA Pittsburgh Healthcare System; Speaker, Novartis. M.R. Smith: Consultant, Amgen, GTx, Merck, and Novartis. K.N. Weilbaecher: Speaker, Novartis. The other authors declare that they have no conflicts.

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