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Advances in Treating Metastatic Bone Cancer: Summary Statement for the First Cambridge Conference

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Abstract

The First Cambridge Conference on Advances in Treating Metastatic Bone Cancer, a symposium held in Cambridge, Massachusetts, October 28 to 29, 2005, was convened to discuss recent advances and research related to the natural history of bone metastases and skeletal complications, bone cancer biology, treatment of myeloma and other solid tumors, and treatment-induced bone loss. The conference format combined brief presentations with extended periods of discussion. The conclusions reached during the 2-day meeting are summarized in this article and presented in more detail in the individual articles and accompanying discussion sessions that comprise the conference proceedings.

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Natural History

The skeleton is both the most common organ affected by metastatic cancer and the site that produces the greatest morbidity for patients. Because breast and prostate cancer are so prevalent, metastatic bone cancer is most often seen in these patients. However, bone metastases are present in a wide range of advanced cancers, including thyroid, kidney, and lung. For many patients, metastatic bone cancer is a chronic condition, with survival from the time of diagnosis varying significantly among the various tumor types. For bone metastases from prostate and breast and in multiple myeloma, median survival time from diagnosis is measurable in years. For advanced lung cancer, it is usually measured in months.

Skeletal morbidity includes pain, hypercalcemia, pathologic fracture, and spinal cord or nerve compression. Prognosis of metastatic bone cancer is influenced by primary tumor site, presence of extraosseous disease, and the extent and tempo of the bone disease. Disease progression is best estimated by a combination of imaging tests and measurement of bone-specific markers. Recent studies have shown a strong correlation between the rate of bone resorption and clinical outcome, both in terms of skeletal morbidity and disease progression or death. Improvements in understanding prognostic and predictive factors are expected to contribute to the delivery of more personalized treatment for individual patients and more cost-effective use of health care resources.

Biology

Bone mass maintenance is a balance between the activity of osteoblasts, which form bone, and osteoclasts, which resorb it. The mechanisms responsible for tumor growth in bone are complex and involve tumor stimulation of osteoblasts, osteoclasts and the response of the bone microenvironment. In addition, estrogen plays a key regulatory role in this cycle of bone remodeling by mediating effects through the estrogen receptor, present on several cell types in the bone.

It is now well recognized that for tumors to metastasize, they must proceed through multiple steps, including primary tumor growth; the release of tumor cells into lymphatic and blood vessels; survival of the tumor cells within the circulation; arrest in the microvasculature of the target organ, leading to extravasation of tumor cells; invasion of target organs; and finally, growth of the tumor at the metastatic site (1,2). Any step in the cascade is potentially a target for therapeutic intervention. For many years, research on metastatic bone cancers focused almost exclusively on tumor cells. However, more recently, bone cell function and its interplay with tumor cells have been considered.

Breast cancer tumors produce many factors that stimulate osteolysis, including parathyroid hormone–related protein, interleukin-11, interleukin-8, interleukin-6, and RANKL (3–8). Recent data support the concept that bone-derived transforming growth factor-β and tumor-derived osteolytic factors, such as parathyroid hormone–related protein, contribute to a vicious cycle of local bone destruction in osteolytic metastases. When transforming growth factor-β is released in active form during osteoclastic resorption, (9) it stimulates parathyroid hormone–related protein production by tumor cells, which then mediates bone destruction by stimulating osteoclasts. Recent data support a role for transforming growth factor-β blockade in the treatment of breast cancer bone metastases and indicate that therapeutic targeting of transforming growth factor-β may decrease the osteolytic bone metastases due to breast cancer by blocking tumor production of osteolytic and growth-promoting factors, such as interleukin-11, parathyroid hormone–related protein, and platelet-derived growth factor.

Prostate cancer, in contrast to breast cancer, has a propensity to metastasize to bone and locally disrupt normal bone remodeling. Although these metastases may appear osteoblastic based on

radiographic appearance, it is clear that bone resorption and bone formation are dysregulated. Recent clinical evidence indicates that both osteoblastic and osteoclastic processes can contribute to the formation and progression of these lesions, even in a single patient. Thus, combination therapy targeting both osteoblasts and osteoclasts should be an effective treatment for osteoblastic bone metastases.

Therapeutic Strategies

Bisphosphonates are highly effective inhibitors of bone resorption. They selectively affect osteoclasts *in vivo* but also have the potential to directly affect tumor cells. These compounds have high affinity for calcium ions and therefore target bone mineral, where they appear to be internalized selectively by bone-resorbing osteoclasts and inhibit osteoclast function. The nitrogen-containing bisphosphonates (alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid) act by inhibiting farnesyl diphosphate synthase, an enzyme of the mevalonate pathway, which disrupts osteoclast function by preventing the prenylation of GTPase signaling proteins. Bisphosphonates that lack a nitrogen have a different mode of action that appears to involve primarily the formation of cytotoxic metabolites in osteoclasts.

Other pathways and molecules that affect bone and tumor growth pathways are also being explored for possible inhibition or blockade. These include RANKL, an important mediator in the pathogenesis of a range of skeletal diseases; the endothelin axis, which plays a multifaceted role in prostate cancer progression; cathepsin K, a key enzyme in collagen breakdown during bone resorption; src, a tyrosine kinase that plays a key role in osteoclast activity; and p38 mitogen-activated protein kinase, which is thought to play a role in cytokine signal transduction.

Treatment for Metastatic Bone Pain

Because most patients with cancer metastatic to the bone experience extreme bone pain, pain management is an important component of disease management. Research studies evaluating the guidelines of WHO for cancer pain relief (10,11) indicate that most patients obtain good pain relief when the WHO protocol for oral analgesic medications is followed (12). Medical management of metastatic bony disease pain typically begins with paracetamol or nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors that are aimed at alleviating inflammatory states associated with bone pain. The potency of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs is similar, but cyclooxygenase-2 inhibitors produce fewer gastrointestinal adverse effects. Despite the availability of effective pain treatments and various pain management guidelines, multiple studies have documented the undertreatment of pain, especially bone pain, in patients with cancer. The most frequently identified barriers to appropriate pain management are physician underestimation of the patient's pain, inadequate pain assessment, and patient reluctance to report pain.

Experimental studies in animal models are providing insight into the mechanisms that drive metastatic bony disease pain that may provide an opportunity to develop targeted therapies. Mechanisms that drive metastatic bony disease pain include tumor-directed osteoclast-mediated osteolysis, tumor cells themselves, tumor-induced nerve injury, stimulation of transient receptor potential vanilloid type I ion channel, endothelin A, and host cell production of nerve growth factor. Current and potential future therapies include external beam radiation, osteoclast-targeted inhibiting agents, anti-inflammatory drugs, transient receptor potential vanilloid type I antagonists, and antibody therapies that target nerve growth factor or tumor angiogenesis. It is likely that a combination of these therapies will be superior to any one therapy alone.

Further research is needed to identify effective treatment for pain related to metastatic bony disease. This research is principally focused on defining the role of osteoblasts in the generation of metastatic bony disease pain, further developing combination therapies, and exploring treatments that target nerve growth factor and tumor angiogenesis. To more effectively treat the bone pain associated with metastatic bony disease, standardization of the scales and types of assessment for metastatic bony disease pain is urgently needed.

Treatment of Bone Metastases and Prevention of Skeletal Morbidity

Beyond therapies for pain, treatment for metastatic bone cancer and skeletal complications includes radiation therapy, radionuclides, interventional methods of stabilization (such as kyphoplasty and orthopedic intervention), and the use of bisphosphonates to inhibit osteolysis. Of all the options currently available to specifically treat cancer-induced skeletal complications, including bone pain, the nitrogen-containing bisphosphonates, including pamidronate and zoledronic acid, are currently considered to be the most effective. The suggested mechanism of action is a direct inhibition of osteoclasts and perhaps also osteoclast precursor cells (13).

Placebo-controlled trials of oral and i.v. bisphosphonates have shown that prolonged administration can reduce the frequency of skeletal-related events by 30% to 40% in breast cancer metastatic to bone and in up to 50% in patients with multiple myeloma (14). However, there are some toxicity concerns with the prolonged use of bisphosphonates, including renal toxicity and osteonecrosis of the jaw. Osteonecrosis of the jaw may occur in patients on long-term bisphosphonate therapy. This complication occurs in ~ 1% of patients yearly on treatment with i.v. agents. It is thought to become more likely if the patient is undergoing any manipulations in the oral cavity, such as tooth extractions and placement of oral implants (15). The role of bisphosphonates on disease progression and full assessment of the effects of their long-term use require further study.

In prostate cancer bone metastasis, endothelins are being investigated as a potential target for inhibition. Atrasentan (ABT-627) is an inhibitor of the endothelin-A receptor and promotes bone formation *in vitro* and inhibits osteoblastic metastases in mice (16). It is currently in phase 3 trials in patients with prostate cancer and bone metastases (17) as well as in patients with rising prostate-specific antigen levels who are expected to develop bone metastases. Although initial clinical results have been disappointing, further studies of atrasentan and other selective endothelin-1 antagonists, such as ZD4054, are ongoing.

Another novel agent in clinical development for the treatment of skeletal breast and prostate bone cancer metastases is the bone-seeking, α-particle-emitting radiopharmaceutical $^{223}RaCl_2$ (Alpharadin). Clinical data indicate that use of ^{223}Ra in single dose or repeated regimens and also after external beam irradiation seems to be safe. Further evaluation is planned to study its role in delaying disease progression and survival in patients with skeletal metastases.

Multiple myeloma is a B-cell malignancy characterized by enhanced bone loss. Bone destruction results from increased osteoclastic bone resorption, which is not accompanied by a comparable increase in bone formation. Consequently, myeloma patients frequently require radiation therapy, surgery, and analgesic medications. Pamidronate or zoledronic acid are now a mainstay of myeloma therapy. Recent advances in bone-seeking radiopharmaceuticals make these attractive candidates to combine with bisphosphonates or radiosensitizing drugs to achieve synergistic effect in myeloma (19).

Although bisphosphonates, particularly pamidronate and zoledronic acid, currently provide the most effective option available to specifically treat cancer-induced skeletal complications,

including bone pain, their effect on disease progression and issues with their long-term use require further study. Ibandronate has been shown to be active in metastasic breast cancer. Several new agents are undergoing clinical evaluation for the treatment and prevention of metastatic bone cancer, including denosumab (AMG-162) and atrasentan (ABT-627), which are in advanced clinical testing, and inhibitors to cathepsin K, src, and p38 mitogen-activated protein kinase, which are much earlier. Future directions for treating metastatic bone cancer are expected to focus on both further enhancement of these targeted therapies and combinations with other tumor-and bone-targeted agents. This multipronged approach is already undergoing considerable study in preclinical models and early clinical investigations.

Prevention of Bone Metastases

In breast cancer, trials of the oral bisphosphonate clodronate have suggested that bone-specific therapy may be an effective adjuvant therapy in patients with operable breast cancer. Clodronate for 2 years significantly reduced the risk of bone metastases, with a significant reduction in mortality (18). This benefit, together with the low toxicity and safety, supports its use as additional adjuvant therapy for patients with primary breast cancer. However, confirmatory trials are required and indeed have completed accrual. Additional clinical trials are in progress to assess optimal duration of therapy, efficacy in other early-stage diseases, such as prostate cancer with a rising prostate-specific antigen, and the relative efficacy of other bisphosphonates.

Treatment-Related Osteoporosis

Hormone therapy for prostate cancer using gonadotropin-releasing hormone agonists and adjuvant hormonal therapy for breast cancer using aromatase inhibitors both contribute to osteoporosis and fracture risk by increasing bone turnover and decreasing bone mineral density. In prostate cancer patients, most studies using gonadotropin-releasing hormone agonists have reported a 2% to 3% decrease yearly in bone mineral density of the hip and spine during initial therapy, and bone mineral density appears to decline steadily during long-term treatment (20).

In addition, chemotherapy often induces primary ovarian failure in premenopausal women, resulting in decreased levels of circulating estrogen and subsequent osteopenia. Women receiving either or both therapies are at an increased risk of the development of osteoporosis and skeletal fractures.

In prostate cancer, estrogen deficiency, rather than testosterone deficiency, appears primarily responsible for the adverse effects of gonadotropin-releasing hormone agonists. In small randomized controlled trials, bisphosphonates (pamidronate and zoledronic acid) and selective estrogen receptor modulators (raloxifene and toremifene) increased bone mineral density in gonadotropin-releasing hormone agonist–treated men. Although no consensus guidelines have been developed, most authors of recent reviews recommend screening for osteoporosis with dual energy X-ray absorptiometry scans, weight-bearing exercise, supplemental calcium and vitamin D, and selective treatment with bisphosphonates for men at the greatest risk of fracture (21,22).

At least two large randomized placebo-controlled fracture studies in gonadotropin-releasing hormone agonist-treated men are ongoing to prospectively define fracture outcomes in men with prostate cancer and assess the efficacy of novel pharmacologic interventions (AMG-162, toremifene) in this setting. In breast cancer, patients who are being treated with hormonal therapies are advised to follow similar guidelines to those listed above for prostate cancer (23,24).

Future Developments

A multitude of possible targets have been identified that play roles in metastatic bone cancer. The question is how many targets need to be addressed and how many should be blocked. Further exploration of the underlying pathophysiology of bone disease is needed to assist in assessing and prioritizing which factors to target and how to target them effectively and to aid development of proof of concept studies. One approach that should be explored is to use smaller clinical studies with more defined clinical end points, keeping in mind that individual patients are different and need specific treatments that take into account the form and stage of metastatic bone disease and tumor type as well as other comorbid conditions.

Multistate modeling, which is a method of analysis represented by multistate diagrams that indicate the finite number of clinical states a patient can occupy during follow-up, is an appealing approach to the analysis of diseases with complex courses, such as metastatic bone cancers. This approach can integrate information on the nature of the disease process, implications of event occurrence on the risk of subsequent clinical events or death, and the cumulative disease burden based on the expected number of events.

In addition, studies are needed to determine how we can better predict which tumors are going to metastasize to bone to select patients for preventative bone targeted therapeutic strategies. Some studies have been done using gene array analysis to try to predict which types of cancers are associated with poor prognosis and poor responses to therapy, but at present no studies have been performed to identify tumors that are most likely to metastasize to bone. More effort needs to be made to try to identify biomarkers in a variety of different tumor types and that have diagnostic, prognostic, or predictive utility.

Combining pharmaceutical agents is going to play an important role in future therapies. Both animal and clinical studies need to be done using bisphosphonates in combination with other agents to try to improve on the benefits already being achieved with current bisphosphonates.

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