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Commentary

Bone-targeted therapy for metastatic breast cancer—Where do we go from here? A commentary from the BONUS 8 meeting

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ABSTRACT

The annual *Bone and The Oncologist New Updates* (BONUS 8) conference focuses on the current understanding and dilemmas in the treatment and prevention of bone metastasis in cancer, as well as novel research on bone homeostasis and cancer-induced bone loss. We present commentaries from experts for their own take on where they feel the field of bone-targeted therapies for metastatic breast cancer is moving, or needs to move, if we are to make further progress.

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1. Introduction

Despite advances in breast cancer treatment, bone remains the most common site of metastasis [1,2] occurring in around 70% of patients with metastatic disease [3]. Bone metastases are incurable and associated with significant morbidity in terms of fractures, pain, and reduced quality of life. Bone destruction occurs from disruption of the finely controlled balance between bone resorption (by osteoclasts) and formation (by osteoblasts), resulting in net bone breakdown [4]. Increased understanding of the pathogenesis of bone disease has resulted in the development of a number of bone-targeted agents (BTAs), the most widely used clinically being inhibitors of osteoclastogenesis and osteoclast activation [i.e. bisphosphonates, or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g. denosumab)] [5].

However, despite the use of these increasingly potent BTAs, progress in terms of absolute reductions in the occurrence of skeletal related events (SREs) is modest, and further basic, translational, and clinical research is clearly needed [6–12].

The Bone and the Oncologist New Updates (BONUS) meeting is an annual Canadian multidisciplinary conference on the interaction

of bone and cancer biology. Each year, clinical oncologists, basic scientists, and other health researchers gather to discuss the discoveries in bone research and their implications for cancer patients [13]. The most recent conference, BONUS 8, was held in Ottawa in April 2013 with featured speakers from across Canada and the United States. Topics of discussion were diverse, and ranged from prevention of skeletal metastases to the exploration of biomarkers as tools to guiding treatment. As part of this meeting's mandate is to ensure publication of findings to as broad an audience as possible this commentary was written to assimilate key presentations from a number of experts in the area and focus on where the field is moving, or needs to move, if we are to make further progress.

2. Bone specific therapy in metastatic disease—should we curb our enthusiasm?

Quite simply the objectives of any therapy should be the prolongation of life and/or improvement of quality of life. All other endpoints are clinically relevant only if they are associated with these goals. We all recognize that bone metastases are common in breast cancer and cause significant morbidity. They may lead to SREs, including pathologic fractures, need for surgery or radiation to bone, spinal cord compression, and hypercalcemia [14]. These complications result in

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loss of autonomy, pain, and consumption of significant healthcare resources. Ultimately they may also lead to decreased survival [15].

Bone-targeted therapy with bisphosphonates and more recently, denosumab, has been seen as an important part of anti-cancer therapy. In the bone microenvironment, bisphosphonates may exert anti-tumor effects via attenuation of tumor adhesion and invasion, and induction of tumor cell apoptosis [16]. This class of drugs may also indirectly suppress tumor proliferation by virtue of their anti-angiogenic effects [17]. Denosumab is an inhibitor of the RANK ligand, a factor that promotes osteoclast differentiation and activation, and interruption of this interaction may lead to decreased bone resorption and destruction [12]. Both bisphosphonates and denosumab have been shown to be effective in reducing SREs [12,18,19].

However, while bisphosphonates and denosumab are effective in preventing and delaying SREs, none have yet shown a beneficial effect on overall or progression free survival [12,20,21]. Moreover, the benefit in terms quality of life for patients with metastatic cancer from the use of these bone-targeted agents is also unclear. While long term follow up of two large trials comparing pamidronate to placebo showed that patients in the pamidronate arm experienced less pain, the overall quality of life was not different between the arms [20]. Similarly, another trial comparing zoledronic acid to placebo showed that while zoledronic acid did improve pain control slightly compared to placebo, it did not improve the overall quality of life for patients on this drug [21]. Lastly, in a trial comparing denosumab to zoledronic acid in metastatic breast cancer, statistical improvements in quality of life was observed with denosumab only at a minority of time points during follow up and the analysis was compromised by the effects of multiplicity [19].

In summary, current evidence suggests that bone-targeted agents reduce morbidity from metastatic disease to bone, and potentially improve quality of life in patients with metastatic breast cancer. As there are costs and potential adverse effects associated with these agents, care should be taken in their use. In addition, further work is needed in the creation of meaningful measures of quality of life in these patients [22].

3. The vicious cycle: not so simple anymore!

Metastatic tumor growth in the bone is affected by a complex network of cellular interactions and effector molecules. The interactions between osteoclasts, osteoblasts, and tumor cells have been shown to drive tumor growth through a “vicious cycle”. In this framework, tumor cells secrete factors such as parathyroid hormone-related protein (PTHrP) that induce osteoblast and osteoclast activity, leading to bone resorption and destruction, release of growth factors such as transforming growth factor (TGF)- β , and subsequent tumor growth and perpetuation of the destructive cycle [23]. What has become clear over the years is that while the “vicious cycle” was a relatively simple concept to explain some interactions occurring in metastatic bone disease and rationale for the development of bisphosphonates and denosumab—the real picture is a lot more complex [7].

Increasingly, the importance of the tumor microenvironment itself in this destructive cycle has come under scrutiny. Cells that are not directly involved in bone remodeling, including lymphocytes, macrophages, and stromal cells may affect tumor growth through their interactions with tumor cells. As part of the bone marrow stromal environment, adipocytes, fibroblasts, and chondrocytes have been implicated in the differentiation and proliferation of both hematopoietic and cancer cells, in part through secretion of pro-resorption cytokines by tumor cells following their engagement with stromal cells via VCAM-1 mediated interactions [24].

Myeloid-derived suppressor cells (MDSC) represent a diverse population of myeloid-lineage cells that includes macrophages, dendritic cells, and granulocytes. They are known to proliferate in the setting of cancer, can down-regulate the immune response [25], and have been linked to multiple aspects of cancer progression, including tumor growth, angiogenesis, and metastasis [26,27]. In a xenograft mouse model, these cells have been shown to differentiate into osteoclasts and accelerate tumor growth and bone destruction [28].

The extracellular matrix (ECM) of the bone is also implicated in the metastatic process. The ECM contains a constellation of proteins and other biomolecules that serve both as a scaffold for mineral deposition, and as signaling molecules that help direct bone formation and resorption [29]. These interactions may become dysfunctional in the setting of metastatic cancer. Bone sialoprotein (BSP) is a major non-collagenous protein in the ECM, and can induce cell adhesion and promote osteoclastogenesis [30]. High BSP levels are seen in multiple cancers, and have been associated with excessive bone resorption in animal models [31]. Indeed, preliminary experiments in a mouse model using siRNA-mediated knockdown of the BSP gene revealed reductions in both osteolysis and tumor incidence [32].

It is clear that the process of bone metastasis involves much more than the model of the vicious cycle itself, and that many types of cells, effector molecules, and the extracellular matrix participate in the development of bone metastases. However, their precise roles have yet to be fully elucidated. Better understanding of their interactions with bone and tumor cells may lead to discovery of novel protective therapies.

4. Bone-specific therapy in metastatic disease—an oncodynamic perspective

Bone metastasis involves the dysregulation of normally tightly controlled bone homeostasis. Tumor cells release paracrine factors that stimulate osteoclast and osteoblast recruitment and differentiation. Bone resorption due to osteoclast activity can liberate growth factors from the bone matrix that can drive further tumor growth [33]. Similarly, growth factors secreted by osteoblasts may also stimulate tumors. This process is associated with significant morbidity including bone loss, pathologic fractures, and cancer-induced bone pain [20].

The underlying biology of cancer metabolism is complex. Multiple biochemical pathways and their associated signaling molecules are affected and dysregulated by cancer. Aberrant signaling in these pathways not only drive tumor growth but can lead to significant symptoms such as pain. This concept of abnormal cues on the physiology of the body in the context of cancer may be termed oncodynamics. Investigation of these abnormal cues may lead to novel therapies for cancer-associated symptoms.

For example, glutamate is increasingly recognized as one of the important dysregulated signaling molecules in cancer biology, especially in the context of bone metastasis. Commonly recognized as an excitatory neurotransmitter necessary for normal brain function, glutamate is also intimately involved in bone metabolism in both health and diseased bone [34]. Multiple cancer cell lines are known to secrete glutamate into the extracellular environment [35]. In vitro models have shown that its secretion by cancer cell lines stimulated osteoblast differentiation, while inhibition of glutamate release led to reduction of the osteoclast population [36]. Specific glutamate receptors present on osteoclasts have been identified, and modulation of these receptors can inhibit glutamate release and bone resorption [37].

Glutamate is also associated with the perception and transmission of pain. Multiple studies involving subcutaneous administration

of glutamate to healthy volunteers revealed glutamate to be a potent dose-dependent inducer of the pain response [38,39]. Given its secretion by cancer cells, tumor-derived glutamate may be involved in the generation or maintenance of cancer-induced bone pain, through direct stimulation of perception of pain or its disruptive effect upon bone homeostasis in the presence of bone metastases.

Lastly, glutamate may also contribute to cancer-associated depression. Major and minor depression can be seen in over one third of cancer patients [40], a rate that is far higher than in the general population [41]. Abnormalities in glutamate levels have been observed in multiple areas of the brain in patients with depression [42]. Compellingly, the glutamate receptor antagonist ketamine has been shown in multiple small studies to produce anti-depressive effects in patients [43]. Whether direct links exist between tumor-secreted glutamate and depression is currently not known but warrants further investigation.

5. Summary

The BONUS conference continues to be a forum that attracts oncologists, basic scientists, and other professionals interested in bone health in cancer. This year's meeting reviewed our current understanding of bone biology and metastasis, as well as ongoing research in the field. What is evident is that we have likely maximized the benefits that patients will receive from current bone-targeted therapies and that the gains from increasingly potent agents while statistically significant are clinically modest [10,44]. If progress in this area is going to be made we need to use the new knowledge we are generating around the complex interactions that occur in bone to develop new treatment strategies. Ultimately we all hope that this will also enhance our efforts at trying to stop breast cancer from spreading to the bones in the first case.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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