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Commentary: Role of Bone-Modifying Agents in Metastatic Breast Cancer

By Gabriel N. Hortobagyi, MD, FACP

Bone is the most frequent target of metastatic breast cancer, and although bone metastases are not life threatening, some of the complications (spinal cord compression, hypercalcemia) can be.¹ More important, bone metastases and their complications can be substantially disabling, require multiple interventions, and are costly to the patient and the health care system. Until about 1990, there were no approved drugs for the management of bone metastases, although there was much interest in agents to control hypercalcemia (calcitonin, vitamin D, mithramycin, etc). In the latter part of the 1980s, exciting reports indicated that bisphosphonates were effective in control of hypercalcemia, and a number of clinical trials were initiated to determine the benefit of these agents in the management of patients with bone metastases. Clinical trials demonstrated that both clodronate and pamidronate had some analgesic effect and reduced the risk of bone-related complications (skeletal-related events), such as pathological fractures, hypercalcemia, and spinal cord compression, while reducing the need for palliative radiotherapy and surgery.²⁻⁵ As a result, these agents were rapidly incorporated into the treatment of patients with bone metastases, first in breast cancer and multiple myeloma and subsequently other cancers that targeted bone. Ibandronate and zoledronic acid followed, with clinical trials demonstrating that the latter was significantly more effective than earlier generation bisphosphonates for control of bone metastases and reduction of skeletal-related events.⁶⁻⁷ Bisphosphonates were shown to be more effective and/or easier to use than previously existing agents (calcitonin, mithramycin) or newer agents with established activity (gallium nitrate). Over a short period of time, bisphosphonates became part of the standard of care for metastatic cancers, and clinical trials were initiated to determine their contribution to curative treatment of primary malignancies. It is clear that the addition of bisphosphonates to multidisciplinary treatment strategies has dramatically altered the clinical course of bone metastases. Hypercalcemia has decreased drastically in incidence and severity, as have bone pain, pathological fractures, and the need for palliative radiotherapy and surgery. This is an important achievement, as patients with bone metastases

live longer than those with metastases to other organs and therefore, their symptoms are present for a longer time, as is the disability they cause.

Although well tolerated, bisphosphonates do have a few adverse effects: infusion-related reactions and hypocalcemia are occasionally seen, although they are self-limited and reversible.⁶ Of greater concern, reports of osteonecrosis of the jaw (ONJ) started to appear and were eventually linked to longer term administration of bisphosphonates.⁸ Renal function impairment was also observed, requiring renal function monitoring with these agents. It was also apparent that bisphosphonates worked for many, but certainly not all, patients with bone metastases and that there were no biomarkers to select those patients most and least likely to benefit. These circumstances set the stage for the development of additional, perhaps better bone-targeting agents. During the development of bisphosphonates, multiple research laboratories markedly expanded our understanding of bone physiology and molecular biology, and indicated novel targets for developing effective therapeutics.⁹ The receptor activator of NF κ B (RANK) and its natural ligand (RANKL) are at the epicenter of this signaling network. Thus, a humanized soluble receptor (osteoprotegerin) was developed to compete with the ligand, and subsequently, a monoclonal antibody against RANKL (denosumab).¹⁰ Clinical trials have thus far shown that denosumab is somewhat more effective than zoledronic acid in metastatic cancers, although neither agent delays progression of bone metastases per se. The denosumab trials have also raised concerns about potential increases in infectious complications and new malignancies in patients taking this drug. This deserves close monitoring over the upcoming years, as rare events tend to accumulate when drugs are used for common indications. It is also important to monitor these events because denosumab, like third-generation bisphosphonates, is going to be tested as part of adjuvant systemic therapy of breast and perhaps other cancers. ONJ was also reported in the denosumab trials, although the more limited experience with this drug does not allow precise quantitation of risk. Certainly, the lessons learned about bisphosphonates

and ONJ should serve us well for minimizing the risk of ONJ in association with denosumab: patients should have a good dental assessment and hygiene before initiating bone-directed therapy.

There have been a few reports of midshaft fractures unrelated to metastatic lesions in patients receiving chronic bisphosphonate therapy, including the administration of bisphosphonates for treatment of osteoporosis.¹¹ It is uncertain whether this represents a causal relationship, and additional, well-designed studies are needed to determine the nature of this association, as well as its pathophysiology. In the meantime, careful monitoring for these rare events is clearly indicated.

The ASCO guidelines group has recently completed the monumental task of updating "The Role of Bone Modifying Agents in Metastatic Breast Cancer."¹ This is an important service to the community of patients and physicians alike, because this is an evolving field and there have been multiple publications since the most recent iteration of these guidelines. It is important to pause here to point out how the ASCO guidelines differ from guidelines developed by other organizations. ASCO has an established, validated process that starts with a comprehensive review of the literature, following a pre-established protocol to identify those studies that contain the appropriate information with which to formulate evidence-based guidelines. That review is distilled into the final group of studies that satisfy the definitions, the results are tabulated, discussed, decisions are made regarding the impact new data have on the standard of care or previous guidelines, and a writing committee develops the guideline document, including the Executive Summary and the practical aids associated with each guideline. The ASCO process takes many months and by nature tends to be conservative in its recommendations. This process differs from that followed by other organizations that base some or all of their guidelines on the consensus of a group of experts, weaving into the discussion those studies that the same experts consider of value. Such guidelines might be developed in a day, and the document to summarize them might be completed in a few additional days. When you read the ASCO guidelines, you need to consider these differences, as well as the differences emanating from basing the literature review on a predefined period of time, and excluding from consideration data that become available after the closing date.

The updated guidelines included denosumab on the basis of controlled trials that have demonstrated the relative efficacy of this drug compared with zoledronic acid. This is a good addition to the guidelines and our armamentarium,

although additional monitoring of its effects will be welcome. The guidelines also included a clear statement about ONJ and its prevention and management. There is much more research to be done in this field: the optimal timing of onset and discontinuation of bone-modifying agents; the optimal dose and schedule, especially for chronic administration; development of biomarkers that identify patients who will (and those who will not) benefit from these drugs; and elucidation of the pathophysiology of the more serious adverse effects and complications, as well as methods to prevent their development. We know these drugs improve bone density; their effects on bone strength have been poorly documented. We think of these drugs as "targeted therapies"; yet, we have no biomarkers to use in assessing which populations to target. Finally, all these agents work in up to 50% of patients with bone metastases; we need to understand why they don't work on the rest, and what strategies can be used to better control bone metastases for all patients.¹²⁻¹³ The fate of patients with bone metastases has improved significantly over the past couple of decades thanks to bone-modifying agents. Our choices are becoming more complex, and we must make sure we use these drugs most effectively while limiting the risks of chronic and serious adverse effects.

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