VOLUME 23 · NUMBER 15 · MAY 20 2005

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Progress in the Management of Bone Metastases: One Continent at a Time?

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Bone metastases are a common extension of breast, prostate, and lung cancers, multiple myeloma, malignant lymphomas, and to a lesser extent, other solid tumors.[1] In addition to pain, bone metastases frequently cause complications such as pathologic fractures, hypercalcemia, and spinal cord compression.[2] These complications have a major impact on quality of life, and their control requires multiple therapeutic interventions. Over the last 20 years, bisphosphonates became an integral part of the management of bone metastases. Bisphosphonates are pyrophosphate analogs with potent antiresorptive activity, based on inhibition of osteoclast activity, recruitment, and differentiation.[3] Multiple clinical trials have demonstrated that bisphosphonates represent the treatment of choice for hypercalcemia of malignancy. Initially pamidronate, then zoledronic acid, became the standard of care for managing acute hypercalcemia. Clinical studies in patients with bone metastases also indicated that bisphosphonate therapy had analgesic effects and produced radiographically detectable sclerotic changes in osteolytic lesions.[4,5] These observations, coupled with anecdotal reports of decreased skeletal complications, led to formal evaluation of bisphosphonates in the management of osteolytic bone metastases more than a decade and a half ago. Clinical trials with clodronate strongly suggested, and randomized trials with intravenous pamidronate clearly demonstrated, that bisphosphonate therapy used in association with standard anticancer interventions reduced the incidence and severity of all skeletal complications, or—as it has become customary to report—"skeletal-related events."[2,4,6] In addition to a dramatic reduction in the incidence of hypercalcemia, these studies also documented significant reductions in pathologic fractures, spinal cord compression, pain, analgesic requirements, and the need for radiation therapy or surgical interventions to treat or prevent fractures.[2,4,7,8] These placebo-controlled randomized clinical trials were critical in establishing efficacy using a number of "soft" end points, such as changes in pain score, analgesic requirements, and even the utilization of specific therapies, such as surgery or radiation therapy. Only such carefully controlled trials could keep patient and physician bias and the placebo effect of treatment from resulting in outcome differences. The results of these trials were compelling enough to facilitate the registration of bisphosphonates as appropriate therapy for the management of osteolytic metastases in North America, Western Europe, and most of the rest of the world. Subsequent clinical trials with zoledronic acid, a more potent aminobisphosphonate, extended these observations to other tumor types and to patients with osteoblastic metastases.[9,10] In patients with breast cancer and multiple myeloma, the studies compared zoledronic acid to pamidronates, which was the established standard of care. These studies demonstrated that zoledronic acid was not only more convenient to use, but was also more effective, further reducing skeletal-related events.

In this issue of the *Journal of Clinical Oncology*, Kohno et al[10a] present the results of a prospective randomized trial of zoledronic acid in the management of bone metastases in Japanese patients. The design is identical to the original studies with pamidronate and clodronate performed more than a decade ago, and the implementation of the study was, by all appearances, impeccable. The results confirm that zoledronic acid is a potent antiresorptive agent that significantly reduces the frequency and severity of skeletal-related events in patients with bone metastases. What have we learned from this trial? We learned that the administration of zoledronic acid to Japanese women with metastatic breast cancer was safe and well tolerated, in keeping with all other studies performed to date anywhere in the world. We learned that zoledronic acid has significant activity in patients with bone metastases, as demonstrated in previous studies.

So was there a need to perform this study and was there justification for this design? The investigators state that this was a registration trial, and the placebo-controlled design was justified by the absence of a registered drug in Japan for this indication. No hypothesis is provided to suggest that this drug or class of drugs would have different efficacy or tolerance in Japanese patients. Is this an example of regulatory inflexibility? Why have Japanese women (and men) been deprived of drugs with proven efficacy to reduce complications of bone metastases and the associated morbidity for a decade (clodronate was registered for this indication in the early 1990s in Europe and pamidronate was approved in 1996 in the US)? Do we need to reinvent the wheel in every country or ethnic group every time a new drug is developed? With several hundred drugs under development in oncology alone, this seems to be a tremendously inefficient process, and from the patients' perspective, an undesirable obstacle to progress. With multiple randomized trials performed in ethnically heterogeneous populations in North America and Europe, there should be a strong biologic hypothesis to justify the need for additional trials in other populations. Perhaps drug regulatory agencies worldwide have a lesson to learn from this sad episode.

Regulatory issues aside, it is still important to review what we still need to learn about this group of effective and well-tolerated compounds. Although bisphosphonates have been routinely utilized for the management of hypercalcemia, Paget's disease, and bone metastases for many years, a number of aspects of their optimal utilization remain unexplored. For instance, what is the optimal time to initiate bisphosphonate therapy for bone metastases? Should we institute bisphosphonate therapy at the first evidence of bone metastases or when the patient becomes symptomatic? Most experts advocate initiation of bisphosphonate therapy at the first documentation of bone metastases; however, this has never been appropriately tested. How long should bisphosphonate therapy be administered? In the absence of clinical trial–based evidence, most clinicians continue bisphosphonate therapy indefinitely. While the anecdotal impression of experts in the field is that this is appropriate, there has been no attempt at determining the appropriateness of such strategy. This is inherently beneficial to companies that produce bisphosphonates, but is it necessary or useful, and does it justify the costs associated with indefinite therapy? Can we identify "responders" and "nonresponders" to therapy? As documented by Kohno et al, a 20% absolute reduction in the percentage of patients with skeletal-related events, while being the largest benefit shown in any bisphosphonate trial in bone metastases, suggests that this is the fraction of patients who benefit. Can we identify this group early by monitoring bone resorption markers or correlating outcomes with gene expression or protein expression profiles? What should we do with patients who are unlikely to respond to or benefit from bisphosphonate therapy? Are there other doses or schedules that would enhance the probability of benefit? What are the mechanisms of bisphosphonate resistance? Are other inhibitors of osteoclast activity, such as gallium nitrate, osteoprotegerin, or parathyroid hormone-related protein–inhibitors able to overcome bisphosphonate resistance?[11] These are just some of the many outstanding questions in this field. Some of these questions should be relatively easy to answer, though they will require sponsorship from federal agencies or foundations, because they would likely be of little interest to the pharmaceutical industry. Other clinical questions, such as the benefits of combining bisphosphonates with other osteoclast inhibitors, will require collaborations between two or more companies, and reducing some of the regulatory obstacles and the complexities of patents and intellectual property. However, the potential outcomes are of major importance to the quality of life of our patients and the judicious use of our resources. Most importantly, these are great opportunities to speed up progress in a field of research with overlapping interests to oncologists and endocrinologists, as well as those interested in molecularly targeted therapies.

Progress in these areas will also be critical if we are to understand the role of bisphosphonates in the adjuvant setting. This role is a complex area, because it combines two independent, but related, opportunities. There is suggestive evidence that newer, potent aminobisphosphonates, especially zoledronic acid, have direct antitumor activity.[12-14] Reports have suggested that zoledronic acid is an inhibitor of geranylgeranyl transferase, an important step in protein prenylation.[15] Another step in this process, farnesylation, is the target of new drug development, and several farnesyl transferase inhibitors are undergoing formal development as antitumor agents.[16] There is also information to suggest that zoledronic acid inhibits angiogenesis, or the production and release of proangiogenic factors.[17,18] Furthermore, it is likely that osteoclast-mediated bone resorption is critical to the establishment of bone metastases, and that inhibition of osteoclast activity would represent a substantial obstacle to this process.[19] Since metastatic cells have defined tissue affinity, it is reasonable to hypothesize that cells with predilection for bone targeting would be unable to establish metastatic colonies in other tissues and would eventually be destroyed by the immune system. Taken together, these various hypotheses suggest that it is reasonable to conduct clinical trials of bisphosphonates in the adjuvant setting.

A very different reason for early introduction of bisphosphonates in the management of patients with early breast cancer is the effect of breast cancer and its therapies on bone mineral density. It has been suggested that breast cancer, even in the absence of bone metastases, is associated with an increased risk of pathologic fractures.[20] Several commonly used therapeutic interventions result in premature menopause, or at least prolonged, reversible

amenorrhea, both indicative of transient or permanent ovarian suppression.[21,22] Other treatments suppress estrogen production in postmenopausal women.[23] All treatments resulting in lower endogenous estrogen levels are associated with increased bone resorption, reduction in bone density, and acceleration of osteoporosis. Since bisphosphonates are potent inhibitors of bone resorption, they are indicated and approved for the management and prevention of osteoporosis. Understanding the role of these drugs in the management of primary breast cancer when added to standard anticancer therapy will be an important question in future trials. For these trials to succeed, it will be important to define optimal doses and schedules, the development of surrogate markers of efficacy to allow monitoring during treatment, and the establishment of whether and to what extent bisphosphonates can contribute to the curative treatment of primary breast cancer. Perhaps the resources currently dedicated to comply with redundant regulatory requirements could be better utilized to develop research programs that would provide reliable answers to the many outstanding questions on the optimal use of bisphosphonates in cancer patients.

Author's Disclosures of Potential Conflicts of Interest

The following author or their immediate family members has indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Honoraria: Gabriel N. Hortobagyi, Novartis. For a detailed description of this category, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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