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GUEST EDITORIAL

Time to put an end to the "one size fits all" approach to bisphosphonate use in patients with metastatic breast cancer?

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Bisphosphonates emerged as an effective treatment for metastatic bone disease in the mid-1990s, and in a relatively short time, they have become an integral component in the palliative care of a range of common malignancies that spread to bone. These generally well-tolerated agents have demonstrated efficacy for reducing skeletal-related events (SREs) and for maintaining and improving quality of life.

It is important to remember that approval for the bisphosphonates was based on their ability to reduce the frequency of SREs (defined as a need for radiotherapy or surgery to bone or the occurrence of pathologic fractures, spinal cord compression, or hypercalcemia of malignancy) and not because of their effects on bone pain or symptom relief. Current clinical recommendations state that treatment with bisphosphonates should be initiated after an initial diagnosis of bone metastases and should be continued in the long term for all patients with metastases to bone[1]. Unfortunately, a "one size fits all" approach to the prescription of bisphosphonates has been adopted, whereby patients are all treated at the same dose and dosing interval regardless of their individual risk of a SRE.

Although patients determined to be at high risk for SREs might derive significant benefit from therapy, this group of patients still experiences a significant number of SREs despite appropriate therapeutic intervention with bisphosphonates. On the other hand, patients at lower risk of SREs are likely being overtreated with current bisphosphonate strategies. The irony cannot be overstated: an 80-year-old woman with hormone receptor–positive disease and a single lytic lesion in the pelvis receives exactly the same dose and dosing interval of bisphosphonate as does a 30-year-old woman with hormone-negative disease that has spread to literally every bone in her body. Clearly something is going wrong in this treatment strategy, and a more individualized approach is needed!

In addition, more appropriate use of the bisphosphonates in a more individualized treatment approach could reduce direct drug costs, toxicity (for example, flu-like syndrome, kidney dysfunction, and osteonecrosis of the jaw), and repeated unnecessary trips to the cancer centre to receive infusional therapy[2].

In this issue of *Current Oncology,* we present the findings from the 2011 BONUS meeting, a symposium that brings together clinicians and scientists working in the bone metastasis field with the intention to discuss and work toward strategies that optimize bone-targeted therapy in patients[3]. One particularly interesting presentation from Dr. Eitan Amir summarized the current approaches and limitations of bone-targeted agents used for cancer therapy–induced bone loss as well as for established bone metastases. He presented preliminary results of a small randomized pilot study comparing the efficacy of a less-intensive regimen of bisphosphonates (every 12 weeks) with the current standard regimen (3–4 weeks) in patients on established pamidronate therapy with a low risk of developing SREs. "Low risk" was defined using a biomarker of bone turnover (C-telopeptide), and the primary endpoint was the proportion of patients maintaining C-telopeptide levels in the lower-risk range over the year of the study. Preliminary results show that the proportion of patients staying in the lower-risk group was the same in both study arms. This study is important because it follows on from a number of other studies that looked at reducing the frequency of bisphosphonates in patients at lower risk of SREs. Most compared bisphosphonate infusions every 12 weeks with standard 3- to 4-weekly bisphosphonate treatment (NCT00320710, NCT00424983). The Bismark trial planned to compare several different treatment regimens based on N-telopeptide levels; however, because of its complexity, the trial suffered from a low accrual rate and closed prematurely (Coleman R. Personal communication, 2011).

Recently, results from an Italian study comparing two bisphosphonate treatment regimens (zoledronic acid every 3–4 weeks compared with every 12 weeks) have emerged (NCT00375427). The patients were entered after 1 year of prior bisphosphonate therapy. The results showed that, in terms of skeletal morbidity

rates, the less-intensive treatment regimen was equivalent to the standard regimen in the overall population of metastatic breast cancer patients. Notably, the study did not use any biomarkers of bone turnover to define SRE risk, and so from a practical standpoint, its findings are highly important[4].

Our own group has been involved in a similar evaluation, the Canadian Breast Cancer Foundation–funded TRIUMPH trial, which is designed to compare the efficacy and safety of standard to every-12-weeks bisphosphonate infusions in lower-risk metastatic breast cancer patients, based on serologic biomarkers of bone turnover. The trial has fully accrued ($n = 68$) a year ahead of schedule and should produce results by the end of 2012[5].

Although the trial is still in its early stages, current data suggest that not all breast cancer patients with bone metastases have to be treated in the same way to achieve maximum benefit. Indeed, many can be treated with markedly less frequent visits. These clinical data have the potential to significantly improve quality of life for patients with lower-risk bone metastases because they would have fewer cancer centre visits to make and their chances of drug-induced adverse events should be significantly reduced. The formal analyses and presentation of these clinical results are still awaited; however, it certainly appears that a period of enhanced and more appropriate and personalized use of supportive care measures is commencing, together with a move away from a "one size fits all" approach to bisphosphonate use in patients with metastatic breast cancer. While awaiting the TRIUMPH trial results, practitioners will also be closely watching the emerging data regarding use of therapies that act as alternatives to bisphosphonates. No conclusive data are currently available with respect to the reducing the frequency of administration of the RANKL antibody denosumab[6]. However, given that the use of longer dosing intervals in bisphosphonate therapy for lower-risk patients is likely to become increasingly common, future dose de-intensification trials with denosumab are urgently needed.

CONFLICT OF INTEREST DISCLOSURES

MC has received honoraria from Amgen and Novartis. None of the other authors has any financial conflicts of interest to disclose.

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