Management of Bone Metastases in Advanced Breast Cancer

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Introduction

Clinicians are challenged to prevent and manage a number of complications from advanced breast cancer that may be either tumor-related or treatment-related. Bone metastases, a significant tumor-related complication that strikes a sizeable number of patients, has been the focus of several recent studies.

Prevalence of Bone Metastases

Bone metastases are present in 60% to 80% of patients with metastatic breast cancer. As the most common site of tumor metastases in these patients, bone metastases result in considerable morbidity, including pain, fractures, hypercalcemia, and spinal cord compression. The clinical manifestations of bone metastases follow from a change of homeostasis in which osteolysis outpaces bone formation, and local prostate- mediated tissue destruction occurs. Bone lesions may be lytic, blastic, or mixed.

Bisphosphonates

As a class, bisphosphonates are pyrophosphate analogues that bind tightly to bone hydroxyapatite. They limit bone resorption and modulate cytokines, actions that may then interfere with cell motility and bone metastases. Clinical trials have demonstrated that bisphosphonates inhibit tumor-induced bone resorption, correct hypercalcemia, reduce pain, and diminish the development of new osteolytic lesions and fractures — all leading to potential improvements in quality of life. These agents are now the treatment of choice, in combination with hydration, for the hypercalcemia of malignancy.

One of the goals over the last few years has been to develop bisphosphonates with an increasingly powerful antiresorption activity but without higher inhibition of mineralization. Some of the developed compounds are 5,000 to 10,000 times more powerful than the original etidronate in inhibiting bone resorption. The gradation of potency evaluated in the rat model is believed to correspond with that found in humans, ie, etidronate (~1x), clodronate (~10x), alendronate (~100 to <1,000x), risedronate (~1,000 to 10,000x), and zoledronate (~>10,000x). One of the goals over the last few years has been to develop bisphosphonates with an increasingly powerful antiresorption activity but without higher inhibition of mineralization. Some of the developed compounds are 5,000 to 10,000 times more powerful than the original etidronate in inhibiting bone resorption. The gradation of potency evaluated in the rat model is believed to correspond with that found in humans, ie, etidronate (~1x), clodronate (~10x), alendronate (~100 to <1,000x), risedronate (~1,000 to 10,000x), and zoledronate (~>10,000x).

Bisphosphonates as Adjuvant Therapy

According to a 1998 report by Diel et al., oral clodronate given at 1,600 mg/day for 2 years as part of adjuvant therapy to women with stage II/III breast cancer led to a decrease in the number of new bone metastases as well as nonskeletal metastases in other sites. Additionally, clodronate was seen to have a potential beneficial impact on survival.

However, Saarto and colleagues of Helsinki University reported contrasting preliminary findings at the 1999 ASCO meeting. Using a trial design similar to Diel et al, the Helsinki group randomized 295 patients with early-stage breast cancer to receive either oral clodronate at 1,600 mg/day for 3 years or no bisphosphonate therapy, along with systemic chemotherapy or hormone therapy. The investigators found an increased risk of metastases and also an increased death rate in patients randomized to receive clodronate vs no clodronate in combination with systemic adjuvant therapy.

Such apparently contradictory results highlight a need for further randomized studies, particularly with regard to bisphosphonate use in adjuvant therapy settings. To further address this question, a randomized trial employing intravenous zoledronate will be conducted under the auspices of the Breast Intergroup. Another trial using clodronate is being planned through the National Surgical Adjuvant Breast and Bowel Project.

Pamidronate vs Placebo

Theriault et al recently reported data evaluating the use of pamidronate vs placebo given at 90 mg as a two-hour infusion every four weeks for 24 cycles. This was the first large clinical trial to evaluate a bisphosphonate in combination with hormonal therapy for patients with metastatic breast cancer. Study endpoints included skeletal complications such as pathologic fractures, spinal cord compression, radiation of bone, surgery to bone, or hypercalcemia. The primary variable of efficacy was skeletal morbidity. The investigators also evaluated bone pain, use of analgesics, quality of life, performance status, bone tumor response, and biochemical parameters. This study established that pamidronate offered a significant therapeutic advantage with regard to a number of endpoints, including pain.

As shown in Fig 1, the mean pain score was 0.5 in patients receiving pamidronate vs 1.6 for patients receiving a placebo, a result which demonstrated that pamidronate was effective in ameliorating pain for patients receiving hormonal therapy for metastatic breast cancer. Pamidronate was also effective in decreasing bone turnover (Fig 2).
In another large clinical trial evaluating pamidronate in the setting of stage IV metastatic breast cancer, Hortobagyi and colleagues evaluated the long-term effectiveness and safety of intravenous pamidronate for up to two years in combination with systemic chemotherapy. In this randomized, placebo controlled, double-blind, parallel-group trial, 185 patients with at least one lytic bone lesion received 90 mg of pamidronate (as two-hour intravenous infusions) every three to four weeks in combination chemotherapy. A total of 197 patients received placebo in combination with systemic chemotherapy. At 15 months, the degree of skeletal complications in patients receiving pamidronate was 46% vs 67% for patients randomized to placebo \((P <.001)\). The benefit proved to be a lasting one, observed again at 24 months after study entry. The same long-term benefit applied to decreasing the need for bone radiation. The Table that summarizes the effects of these agents on bone markers. Pamidronate patients had a negative percent change in turnover markers for bone compared with patients receiving placebo, who had an increase in the bone turnover markers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pamidronate</th>
<th>Placebo</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Urinary hydroxyproline-creatinine</td>
<td>116</td>
<td>-20</td>
<td>109</td>
</tr>
<tr>
<td>Urinary calcium-creatinine</td>
<td>117</td>
<td>-27</td>
<td>109</td>
</tr>
<tr>
<td>Serum bone alkaline phosphatase</td>
<td>114</td>
<td>-29</td>
<td>107</td>
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These data provide evidence of a significant improvement in patients with lytic bone lesions who receive bisphosphonates in combination with systemic therapy, either in the form of hormonal therapy or chemotherapy.

A controversy persists over when bisphosphonate therapy should be started, given both the cost of the agents and its somewhat inconvenient method of administration. In this regard, these randomized clinical trials seem to argue in favor of bisphosphonate use at an early juncture: patients with as few as one lytic bone lesion were among those who derived the most benefit in terms of decreased risk of skeletal complications, including the need for radiation therapy. The recommendation of many physicians is that if lytic bone lesions can be seen, bisphosphonates should be considered a part of the standard management for patients with metastatic breast cancer. An important contribution could be made to the therapeutic ease of use of bisphosphonates if shorter-duration intravenous administration and/or oral agents were developed.

References


**Discussion**

Dr Horton: What do you recommend for a patient who presents with asymptomatic bone metastasis and perhaps a few osteoblastic lesions? Is this patient a suitable candidate for bisphosphonate treatment?

Dr Perez: The trials performed to date have not included patients with purely blastic lesions. They have been designed especially for patients with lytic bone lesions. It is tempting to think that there will be both blastic and lytic turnover in these patients, but benefit has not been established in clinical trials in breast cancer. Studies of that nature are being performed in patients with prostate cancer patients with blastic lesions, but I am not aware of any results.

Dr Horton: How would you manage an advanced breast cancer patient with a couple of small asymptomatic osteoblastic lesions?

Dr Muss: It would not be unreasonable to initiate bisphosphonate therapy, but I think if the patient had a few blastic lesions and a very long free interval and were otherwise doing well, I don’t know if I would feel compelled to bring her to the clinic every three to four weeks to give them pamidronate. It would be reasonable to consider it if the bone disease progressed beyond a couple of asymptomatic blastic lesions.

Dr Horton: Edith, if you have started treatment with a bisphosphonate and the disease progresses — the patient gets some fractures and increasing pain — do you stop the treatment or do you continue it?

Dr Perez: This has not been addressed in clinical trials, but these are really the only agents that have ever been shown to decrease the potential for skeletal metastases in patients with breast cancer. So we tend to continue therapy even if we see one skeletal event, essentially hoping that these agents will prevent the development of more complications. But there are no clinical trial data supporting what to do after the occurrence of first skeletal event of a patient on the bisphosphonate.

Dr Muss: I agree with Edith. I also think it’s important to consider the context of the patient’s other clinical problems. If it is solely bone metastases, which probably occur in approximately 20% percent of patients, this will dominate their course with metastatic breast cancer, and it might be reasonable to leave them on the bisphosphonate.

Certainly if patients have other metastases that are actively progressive, such as pulmonary or liver — and if they are obviously declining, and you’re able to control their bone pain pharmacologically — bringing them back for infusions of bisphosphonates is probably not necessary. But it’s still an open question as to whether you are retarding the metastases or whether they are progressing with the same natural history they would have with no treatment.

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