The Role of Bisphosphonates in Early- and Advanced-Stage Breast Cancer: Have We Finally Optimized Care?

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Bisphosphonates have played an important role in the treatment of breast cancer, mainly in patients with bone metastasis, by reducing the risk of fracture, spinal cord compression, and hypercalcemia.

Introduction

Bone is the primary site for breast cancer metastasis, representing a significant burden of disease and leading to fractures, spinal cord compression, pain, and hypercalcemia.[1] Breast cancer patients often live many years with skeletal metastasis, with an average survival of 4 years.[2] The propensity of breast cancer to metastasize to bone likely represents a complex interaction between metastatic cancer cells, bone, and the intermediary local microenvironment. Bone-targeted therapy with bisphosphonates has greatly improved the systemic management of patients with advanced breast cancer by decreasing the frequency and morbidity of skeletal-related events (SREs). We also now have emerging evidence that demonstrates the benefit of adjuvant bisphosphonates in preventing bone metastasis and improving breast cancer–specific survival among postmenopausal women who undergo adjuvant therapy.

Mechanism of Action

Bisphosphonates are structural analogs of pyrophosphate that embed into bone, binding to hydroxyapatite and inhibiting osteoclast activity and survival.[3,4] Thus, bisphosphonates can inhibit tumor-mediated osteolysis driven by osteoclast activation. There are two classes of bisphosphonates—(1) nitrogen-containing and (2) non–nitrogen-containing—which differ in potency and direct mechanisms of action. Bisphosphonates have also been shown to have effects independent of their antiresorptive properties, including evidence of immune-modulatory properties. Bisphosphonates may also have associated antiproliferative and antiangiogenic effects.[5] These multiple mechanisms of action speak to the importance of bisphosphonates as bone-modifying agents and likely contribute to their significant clinical benefit in the treatment of breast cancer.

Role of Bisphosphonates in Advanced-Stage Breast Cancer

Efficacy

Strong evidence supports the role of bisphosphonates in the treatment of advanced breast cancer. A Cochrane Collaboration systematic review and meta-analysis of 9 studies, which included 2,806 patients, demonstrated that bisphosphonates decreased the SRE rate by 15% compared with placebo in women with breast cancer who had bone metastasis (relative risk [RR] = 0.85; 95% confidence interval [CI], 0.77–0.94).[6] All bisphosphonates were effective (clodronate, pamidronate, ibandronate, and zoledronic acid) and reduced SREs by 20% to 40%, depending on the agent (Table 1).[7-14] Because of the differing study populations, we should be cautious in drawing conclusions regarding the superiority of one agent over another; however, zoledronic acid had the lowest risk ratio, 0.59 (95% CI, 0.42–0.82). No significant difference was seen between oral agents (RR = 0.84; 95% CI, 0.76–0.93) and intravenous agents (RR = 0.83; 95% CI, 0.72–0.95). Only one clinical trial involving zoledronic acid was included in this subanalysis, however.[7] The Cochrane Collaboration meta-analysis does not show an overall survival benefit for the use of bisphosphonates in women with breast cancer and bone metastasis (RR = 1.01; 95% CI, 0.92–1.11). In addition, the review does not show consistent improvement in global quality of life or improvement in bone pain associated with bisphosphonate therapy. A number of studies have compared specific bisphosphonates directly against one another. There
are no large prospective controlled trials comparing the effectiveness of oral clodronate with that of pamidronate. One small study suggests the potential superiority of pamidronate over clodronate in reducing the risk of vertebral fractures and improving self-reported pain scores.[15] However, the results of this study were never fully published. Pamidronate has also shown superiority over intravenous clodronate in the treatment of malignant hypercalcemia.[16] A large study compared the long-term safety and efficacy of zoledronic acid and pamidronate.[17] The number of SREs in the zoledronic acid and pamidronate groups were similar: 46% and 49%, respectively. The skeletal morbidity rate was lower in patients receiving zoledronic acid (0.90 events per year, compared with 1.49), but this did not reach statistical significance (P = .125). However, a multiple-event analysis showed a significant 20% decrease in SREs with zoledronic acid as compared with pamidronate. The safety profiles of both agents were similar. The recent Zoledronate Versus Ibandronate Comparative Evaluation (ZICE) trial compared oral ibandronate and zoledronic acid and did not conclude noninferiority.[18] The annual SRE rate was 0.50 with ibandronate (95% CI, 0.45-0.55) and 0.44 with zoledronic acid (95% CI, 0.39-0.48). Less renal toxicity was seen in the ibandronate arm.

In a large randomized controlled trial that included more than 1,000 patients, the effectiveness of zoledronic acid was compared with that of denosumab, a monoclonal immunoglobulin G2 antibody that inhibits activation of the receptor activator of nuclear factor kappa-B ligand (RANKL). This study showed the superiority of denosumab in delaying the time to first SRE (hazard ratio [HR] = 0.82; 95% CI, 0.71-0.95; P = .01) and time to subsequent SREs (rate ratio = 0.77; 95% CI, 0.66-0.89; P = .001).[19] However, overall survival, disease progression, and rate of adverse events were similar between the groups. Only a very modest improvement in health-related quality of life was noted, favoring the use of denosumab.[20]

The National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) are consistent in recommending either zoledronic acid or denosumab.[21-23] The recommended dosage of zoledronic acid is 4 mg every 3 to 4 weeks. The current NCCN task force report and ASCO guidelines also list pamidronate as an alternative choice of therapy.[21,23]

Side effects and toxicity

The side-effect profiles of bisphosphonates and denosumab are clearly established, and both are generally well tolerated. Bisphosphonates may transiently cause an influenza-like reaction and fever following administration. A number of bisphosphonates are associated with a risk of renal toxicity and may lead to an elevation in serum creatinine in approximately 5% to 10% of patients, particularly those receiving zoledronic acid.[17,24] The risk of renal toxicity appears to be related to dose, route of administration, and hydration and may be lower with oral bisphosphonates.[25] Clinical practice guidelines recommend lengthened infusion times and dose reductions in the setting of renal insufficiency with a creatinine clearance between 30 and 60 mL/min.[21] Treatment is not usually recommended in patients with a creatinine clearance ≤ 30 mL/min. The development of long-term renal dysfunction or failure, especially requiring dialysis, is rare.[26]

There is a small risk of osteonecrosis of the jaw with bisphosphonates and denosumab, which appears to increase with cumulative long-term therapy.[27,28] Atypical fractures, usually subtrochanteric and diaphyseal fractures of the femur, have also been reported with long-term bisphosphonate use.[29] Denosumab poses a risk of severe hypocalcemia, which may result in serious and potentially life-threatening cardiac arrhythmias.[30,31] Therefore, calcium and vitamin D supplementation is required, and denosumab is contraindicated in patients with severe renal impairment. Denosumab is also given by subcutaneous injection, which may be more advantageous than intravenous infusion.

Choosing wisely

Cost-effectiveness remains a major issue for bone-modifying agents, given their high cost and the need for long-term use. Bisphosphonates have demonstrated clear cost-effectiveness compared with best supportive care by decreasing the rate of skeletal complications and preventing the associated need for hospitalization, radiation, and surgery.[32] Multiple bisphosphonates and denosumab are now available to treat bone metastasis, which has led to much debate—particularly in government-funded or resource-limited healthcare systems—about which agents represent the best value. In Table 2, we have outlined approximate drug and administration costs for clodronate, pamidronate, zoledronic acid, and denosumab at our center (based on Canadian pricing). Analyses have shown that oral agents such as clodronate and ibandronate appear more cost-effective compared with intravenous bisphosphonates; however, oral agents are less potent than intravenous
bisphosphonates and may have inferior efficacy.[33,34] Studies of the cost-effectiveness of zoledronic acid and denosumab have also shown conflicting results.[35-37] Overall, bisphosphonates have clearly documented cost-effectiveness despite their high direct individual drug costs. The incremental benefit of one agent over another is likely less important than establishing long-term compliance with therapy. Therefore, side effects, ease of administration, and affordability should guide patient and physician choices. Direct comparisons of specific agents are also difficult because drug prices will continue to change over time and also across countries, especially once generic drug formulations become available. There is also emerging evidence to support less frequent dosing schedules for intravenous bisphosphonates, which would greatly improve cost-effectiveness and affordability, allowing for more wide-scale use among breast cancer patients.

Interval dosing and duration of therapy

The frequency of administration of intravenous bisphosphonates has been questioned based on pharmacokinetics and long-term bone deposition. The ZOOM and OPTIMIZE-2 trials randomized patients with metastatic breast cancer to every-4-weeks or every-12-weeks dosing schedules of zoledronic acid after 1 year of standard bisphosphonate therapy.[38,39] The results of the ZOOM trial showed a skeletal morbidity rate of 0.22 (95% CI, 0.14–0.29) with the standard every-4-weeks dosing schedule vs 0.26 (95% CI, 0.15–0.37) with the every-12-weeks maintenance dosing schedule. The ZOOM study does show relative clinical equivalency; however, statistical noninferiority was not proved because of the small sample size.[38] The recent OPTIMIZE-2 trial did demonstrate noninferiority: The SRE rate was 22% with an every-4-weeks dosing schedule vs 23.2% with an every-12-weeks maintenance dosing schedule (difference: −1.2%; 95% CI, −7.5% to 9.8%; \( P = .724 \)).[39] Patients in the every-12-weeks group had fewer renal adverse events and no reported instances of osteonecrosis of the jaw. This promising every-12-weeks maintenance dosing strategy will further improve the cost-effectiveness of bisphosphonates and reduce the risk of cumulative dose toxicity. Further study is needed to determine whether denosumab could be used in a similar maintenance dosing strategy.

In contrast, the BISMARK trial did not meet its noninferiority endpoint.[40] This was partially related to poor enrollment; however, the study authors also concluded that the marker-adapted dosing strategy may in fact be suboptimal. The choice of dosing strategy was based on measurement of urinary N-telopeptide of type 1 collagen (NTX), a commonly used biomarker of bone turnover and remodeling.

Clinical practice guidelines could adopt this every-12-weeks maintenance bisphosphonate dosing strategy once the ZOOM and OPTIMIZE-2 study results are fully published. A number of centers have already adopted this maintenance dosing schedule based on the preliminary results that show clinical equivalence. The large ongoing Cancer and Leukemia Group B (CALGB) 70604 trial is investigating every-4-weeks vs every-12-weeks dosing schedules of zoledronic acid in breast cancer patients with newly diagnosed bone metastasis.[41] This will help clarify whether every-12-weeks dosing schedules for intravenous bisphosphonates should become the standard of care for the treatment of bone metastasis.

The necessary duration of bisphosphonate therapy also remains unclear. For now, treatment with a maintenance strategy until there is a significant decline in the patient’s performance status would be reasonable. Most clinical trials have not used bisphosphonates for durations longer than 2 to 3 years. Long-term use of bisphosphonates in the setting of osteoporosis has raised concern about subtrochanteric and femoral shaft fractures.[29] Therefore, further study is needed to define the exact duration of therapy in the context of metastatic cancer, especially as overall survival with metastatic disease continues to improve.

Summary

Overall, treatment decisions should be individualized according to each patient’s clinical presentation, comorbidities, performance status, and optimal method of administration. Oral bisphosphonates such as clodronate and ibandronate are reasonable treatment alternatives for patients with limited bone disease who wish to avoid repeated hospital visits for injections or intravenous infusions. They are also good alternatives for resource-limited countries, where the higher costs of pamidronate, zoledronic acid, and denosumab may be prohibitive. For patients who present with more advanced disease or hypercalcemia or who prefer more aggressive management, we would recommend zoledronic acid or denosumab because of superior relative efficacy. We believe an every-12-weeks maintenance dosing schedule for zoledronic acid could be recommended after 1 year of therapy in patients with otherwise stable bone disease. We also look forward to future
studies that may establish every-12-weeks dosing schedules as the standard of care for all patients with metastatic bone disease. This may make zoledronic acid a more attractive treatment option because of both patient convenience and cost to the healthcare system, compared with denosumab.

**Role of Bisphosphonates in Early-Stage Breast Cancer**

The use of bisphosphonates in early-stage breast cancer has been more controversial. A number of studies have proposed that bisphosphonates alter the local tissue microenvironment and exert anticancer effects that may delay or prevent the establishment of bone metastasis. Bisphosphonates have been clearly shown to reduce the rate of bone loss associated with breast cancer treatment. However, studies have been conflicting regarding their role as an adjuvant anticancer therapy. Currently, clinical practice guidelines do not recommend the use of bisphosphonates in early-stage breast cancer either to prevent the formation of bone metastasis or to improve survival outcomes.[21-23] However, these guidelines need to be updated to reflect more recent advances in knowledge.

**Clodronate**

The earliest adjuvant trials in early-stage breast cancer patients used oral clodronate at a dosage of 1,600 mg/d for 2 to 3 years. Major trials are outlined in Table 3.[42-45] The original study by Diel et al[46] in 1998 showed great promise, with significant reductions in bone and visceral metastasis and improvement in overall survival. Of note, this study was conducted in a group of high-risk breast cancer patients with documented tumor cells within the bone marrow before the start of adjuvant therapy. Long-term follow-up at 8.5 years showed the overall survival benefit was maintained; however, the reduced incidence of bone and visceral metastasis was no longer observed.[42] The results of subsequent studies using adjuvant clodronate have been inconsistent. The largest study to date investigating adjuvant oral clodronate in breast cancer is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B34 trial, which enrolled more than 3,000 patients.[45] This trial was originally negative for all outcome measures, including bone metastasis-free interval, recurrence-free survival, and overall survival. However, subgroup analysis in postmenopausal women did show a 25% improvement in recurrence-free survival. This included reductions in the development of both bone and visceral metastases. No overall survival benefit was demonstrated in postmenopausal women, probably because of the low event rate observed in trial participants.

**Zoledronic acid**

More recent studies using zoledronic acid in the adjuvant treatment of breast cancer are summarized in Table 4.[47-49] These studies have also had mixed results but have provided more clarity on the role of bisphosphonates in the adjuvant setting. The similarity of the overall results to results of previously reported studies using oral clodronate suggests a benefit for adjuvant bisphosphonate therapy in postmenopausal women. The ZO-FAST trial showed a significant benefit for early vs delayed use of zoledronic acid in postmenopausal women, with improved disease-free survival (HR = 0.66; 95% CI, 0.44–0.97; \( P = .038 \)). No overall survival benefit was observed (HR = 0.69; 95% CI, 0.42–1.14; \( P = .15 \)).[49] The AZURE trial was negative for its primary and secondary survival outcomes, except for a significant reduction in the development of bone metastasis (HR = 0.81; 95% CI, 0.68–0.97; \( P = .02 \)). However, a preplanned subgroup analysis did report a significant improvement in disease-free survival in postmenopausal women.[48] Therefore, the overall negative study results likely reflect the significant proportion of premenopausal women enrolled in the trial who did not derive any benefit from adjuvant zoledronic acid. The Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12), conducted in premenopausal breast cancer patients undergoing ovarian suppression, did report a significant improvement in disease-free survival (HR = 0.68; 95% CI, 0.51–0.91; \( P = .009 \)).[47] This benefit may be attributed to the associated use of ovarian suppression, which created an artificial postmenopausal state in these young women. Overall, these three large trials were consistent in demonstrating a clinical benefit in postmenopausal women and in premenopausal women undergoing ovarian suppression.

**Early Breast Cancer Trialists’ Collaborative Group**

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis provides greater clarity about the role of adjuvant bisphosphonate therapy in breast cancer. The EBCTCG meta-analysis, which included 17,709 women treated with adjuvant bisphosphonates, indicated a significant improvement in the prevention of both distant disease recurrence (18.4% vs 21.9%;
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The improvements in breast cancer mortality (15.2% vs 18.3%; absolute net gain +3.1% [SE, 1.3]; log rank 2P = .0004) and all-cause mortality (21.5% vs 23.8%; absolute net gain +2.3% [SE, 1.5]; log rank 2P = .0007) were also significant. In this analysis, women aged > 55 years whose menopausal status was unknown were classified as postmenopausal. A subgroup analysis according to strictly defined menopausal status is described in Table 5. These results translate into a 34% relative risk reduction in bone recurrence (P = .00001) and a 17% relative risk reduction in breast cancer death (P = .004) in postmenopausal women. No significant reduction was seen in recurrence outside bone. Similar benefits were observed with clodronate, compared with aminobisphosphonates such as zoledronic acid. Benefits were similar irrespective of estrogen receptor status, nodal status, and prior use of chemotherapy. No clear benefit was shown for adjuvant bisphosphonate therapy in perimenopausal or premenopausal breast cancer patients.

The reason for the difference in the effects of adjuvant bisphosphonate therapy in premenopausal and postmenopausal women is unclear. We can hypothesize that reduced bone strength caused by menopause and aging may increase susceptibility to the development of metastasis. In addition, the anticancer effects of bisphosphonates may be influenced by age- and estrogen-dependent changes to the local bone microenvironment. The ABCSG-12 study found that young women undergoing ovarian suppression may achieve a benefit similar to that of postmenopausal women. Our understanding of the exact reason for these differences is poor, and further translational research is needed in this area.

Choosing wisely

The cost-effectiveness of adjuvant bisphosphonate therapy in improving breast cancer survival has not yet been analyzed on the basis of the EBCTCG meta-analysis. Economic analysis of the ABCSG-12 study, conducted in Germany, did demonstrate that adjuvant bisphosphonate therapy is cost-effective based on clinical efficacy and quality of life measures.[51] Based on the EBCTCG meta-analysis, the number needed to treat (NNT) for adjuvant bisphosphonate therapy to prevent breast cancer mortality among postmenopausal women is only moderately favorable. (The NNT for breast cancer mortality is 53, calculated from Table 5.) However, given the high costs of metastatic breast cancer treatment, adjuvant bisphosphonate therapy will likely meet cost-effectiveness standards in most developed countries.

Summary

The use of adjuvant bisphosphonate therapy has now been demonstrated to reduce the development of bone metastasis, distant recurrence, and breast cancer mortality among postmenopausal women. These results are practice changing and will help continue to improve the ongoing care of women with breast cancer. We eagerly await the full publication of the EBCTCG meta-analysis. Current clinical practice guidelines could be revised to recommend either clodronate, 1,600 mg daily, or zoledronic acid, 4 mg every 6 months, for 3 to 5 years. The maximum duration of therapy should be 5 years at the most, given current data. We do not recommend longer dosing schedules because of concerns about long-term safety after 5 years of use, which have been reported in patients receiving treatment for osteoporosis. Bisphosphonates also have the added benefit of protecting bone health in postmenopausal women, especially in those receiving aromatase inhibitor therapy.

Conclusion

The past few years have helped provide clarity about the role of bisphosphonates in the treatment of breast cancer. Bisphosphonates continue to play a very important role in the prevention of SREs and hypercalcemia in patients with advanced disease. Zoledronic acid appears to be the most efficacious agent, although many reasonable oral and intravenous options exist for patients and physicians. We could now adopt an every-12-weeks maintenance dosing strategy for intravenous bisphosphonates in women with metastatic disease after 1 year, based on the ZOOM and OPTIMIZE-2 trial data. Therapy should continue until the patient’s health significantly declines. There are no strong data to guide treatment beyond 5 years. The EBCTCG meta-analysis has now also shown the important survival benefit of using adjuvant bisphosphonate therapy for postmenopausal breast cancer. Treatment may also be offered to premenopausal patients undergoing ovarian suppression. Adjuvant therapy leads to considerable benefit by preventing bone metastasis and improving breast cancer...
survival. Future research should continue to focus on biomarker development to guide bisphosphonate therapy. Attempts to date have not been successful. Hopefully, in the coming years we will develop a useful biomarker or genomic signature to optimize patient selection for adjuvant therapy. We also need to develop improved diagnostic imaging and biomarkers to evaluate the response to treatment in patients with established bone metastasis. This will help identify bisphosphonate resistance and improve our ability to determine both the dosing frequency and the duration of necessary therapy. These advances will allow us to build on our recent successes and achievements in the treatment of metastatic breast cancer with bone metastasis.

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Table 5: Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) ...

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