Management of Bone Metastases in Breast Cancer

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Opinion statement

Patients with advanced breast cancer who develop bone metastases suffer an ongoing risk of skeletal complications that can have a significant impact on their quality of life (QoL). These complications include bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy (HCM), a potentially life-threatening condition. Treatment options include radiotherapy to palliate bone pain and/or prevent impending fracture, orthopedic surgery to prevent or repair fractures, analgesics, and bisphosphonates, which can significantly reduce the risk of skeletal complications and delay their onset. Of the known bisphosphonates, zoledronic acid is the most potent. Since its regulatory approval in the United States and Europe in 2001, zoledronic acid (4 mg by 15-minute infusion) has become widely used and has replaced pamidronate (90 mg by 2-hour infusion) as the standard of care for treating bone metastases from breast cancer and bone lesions from multiple myeloma. Zoledronic acid has also demonstrated significant long-term benefits in randomized trials in prostate cancer and other solid tumors, whereas other bisphosphonates have failed. In long-term, phase III clinical testing, zoledronic acid provided significant treatment benefits beyond those of pamidronate in patients with breast cancer and demonstrated a safety profile comparable with pamidronate. Therefore, zoledronic acid is now recommended from the first diagnosis of bone metastasis. Other intravenous bisphosphonates include clodronate and ibandronate. Both are approved in Europe, but their efficacy relative to pamidronate and zoledronic acid is not known.

Introduction

The 5-year worldwide prevalence of breast cancer is almost 4 million patients [1]. Metastatic disease develops in approximately half these patients and involves the skeleton in 65% to 75% of cases [2••]. Bone metastases can cause severe bone pain and debilitating complications. After the initial diagnosis of bone metastases, patients with breast cancer survive for a median of approximately 2 years, [2••] a period at chronic risk for skeletal morbidity. Without bisphosphonate therapy, these patients experience an average of three to four skeletal complications each year [3,4••]. Delaying or preventing these skeletal complications provides meaningful clinical benefit [5•].

Patients with bone metastases from breast cancer may receive chemotherapy, hormonal therapy, radiotherapy, surgery, and bisphosphonate therapy. This review provides an overview of treatments and focuses on the evidence supporting the use of new-generation bisphosphonates in patients with breast cancer. The potential of bisphosphonate therapy to prevent bone loss and the development of bone metastases when administered to patients with early-stage disease is also discussed.

Treatment

Diet and lifestyle

- Metastatic tumor cells secrete factors that stimulate osteoclasts, causing focal bone loss. Therefore, supplements alone are unlikely to prevent skeletal complications. However, daily supplements of calcium (500 mg) and vitamin D (400–500 IU) are recommended to minimize the risk of serum ion fluctuations and to maximize treatment effects in patients receiving treatment with bisphosphonates.
- Because skeletal morbidity is caused by the interaction of tumor and bone, lifestyle changes cannot effectively prevent skeletal complications in patients with malignant bone disease. Lifestyle changes such as self-examination, regular gynecologic visits, and mammography are recommended to aid in early detection of breast cancer, and early treatment may reduce the risk of developing advanced metastatic disease.

Surgery

- The primary goal of orthopedic surgery in patients with breast cancer is to prevent or delay pathologic fractures or spinal cord compression. Therefore, bone lesion progression should be monitored regularly.
- Patients who develop large osteolytic lesions on weight-bearing areas should receive surgical stabilization. Because of a significant correlation with fracture risk, prophylactic surgery is warranted in patients with greater than 30 mm axial cortical involvement [6]. Patients with vertebral lesions should be assessed for impending spinal cord compression, which can be prevented with a support frame or surgical fusion.
- After pathologic fractures have occurred, orthopedic surgery may stabilize bones (*eg*, by the insertion of a nail or a rod) and may facilitate healing. Percutaneous vertebroplasty may be effective in patients who have experienced painful vertebral collapse [7].
- External-beam radiotherapy is often combined with surgery to bone. Healing from surgical intervention should be completed before radiotherapy is commenced [8•].

Radiotherapy

- Radiotherapy (external-beam or radiopharmaceutical) can provide temporary palliation of bone pain and stabilization of bone lesions [8•]. Often patients will have some recalcification of osteolytic lesions following radiotherapy.
- Also, external-beam radiotherapy may prevent or delay pathologic fractures, spinal cord compression, and progression of bone lesions.
- Localized radiotherapy is effective in patients whose pain is limited to a single site. Both single-dose and fractionated radiotherapy are effective for this indication [8•]. However, repeated use for the same target area is contraindicated because of damage to normal tissue, limiting the utility of radiotherapy for recurrent pain.
- Palliation of diffuse metastatic bone pain may require broad hemibody or magnafield irradiation. Single-fraction radiotherapy—6 to 7 Gy to the upper or lower body, followed by 6 to 8 Gy to the remaining portion of the body 4 to 6 weeks—alleviates pain in most patients, usually within 24 to 48 hours [8•]. However, radiotherapy is associated with significant

myelosuppression, especially for whole-body treatments. Additionally, most patients develop nausea, vomiting, and diarrhea. Alopecia and pneumonitis are also common after upper body irradiation. Nonetheless, radiotherapy can delay cancer progression and the requirement for additional therapy.

- In addition to supportive care for gastrointestinal toxicity and myelosuppression, patients who receive radiotherapy should be counseled about the possibility of acute and chronic fatigue, common side effects of radiotherapy that are frequently underestimated, underreported, and undermanaged [9].
- Radiopharmaceuticals can also palliate bone pain, improve quality of life (QoL), and reduce the need for analgesics. Administered intravenously (IV), radiopharmaceuticals become concentrated at sites of bone remodeling. Improvements in pain and QoL were reported in 89% of patients with breast cancer who received strontium chloride 89 therapy. However, responses took up to 3 weeks, and up to 20% of patients developed transient but painful flare responses [8•]. Therefore, patients with expected survival of less than 3 months are not candidates for this therapy. Investigations of other radioisotopes and formulations are currently underway.

Pharmacologic treatment

Chemotherapy

- All patients with advanced metastatic disease should receive effective systemic anticancer therapy. Chemotherapy or hormonal therapy can palliate bone pain and may delay the onset of skeletal complications by delaying disease progression.
- For patients with bone metastases, cytotoxic chemotherapy or hormonal therapy is usually insufficient to prevent skeletal complications [4••].
- Bisphosphonates should be administered concomitantly with antineoplastic therapy to reduce the incidence of skeletal complications and the need for palliative treatments [10].

Nitrogen-containing bisphosphonates

- All bone metastases are associated with focal increases in bone resorption, which is the underlying cause of skeletal morbidity. Patients with breast cancer and bone metastases are especially at high risk of skeletal complications compared with patients with other malignancies (Fig. 1) [11].
- Bisphosphonates bind to bone surfaces and potently inhibit osteoclast-mediated bone resorption [12]. Bisphosphonates disrupt osteoclast metabolism and induce programmed cell death (apoptosis) [13]. First-generation bisphosphonates (*eg*, clodronate and etidronate) have lower potency than newer agents [12]. Moreover, because of limitations in efficacy, bioavailability, and tolerability of oral bisphosphonates, IV therapy appears to be the most effective route for bisphosphonate therapy [10]. Therefore, this review will focus on the IV bisphosphonates that have been introduced into clinical practice over the last 10 years.
- Skeletal morbidity from malignant bone disease occurs in complicated and variable patterns [5•]. Early clinical trials assessed pain levels but recent clinical trials have used a composite endpoint. The skeletal-related event (SRE) is defined as pathologic fracture, spinal cord compression, the requirement for surgery to bone to fix or prevent fractures, or the

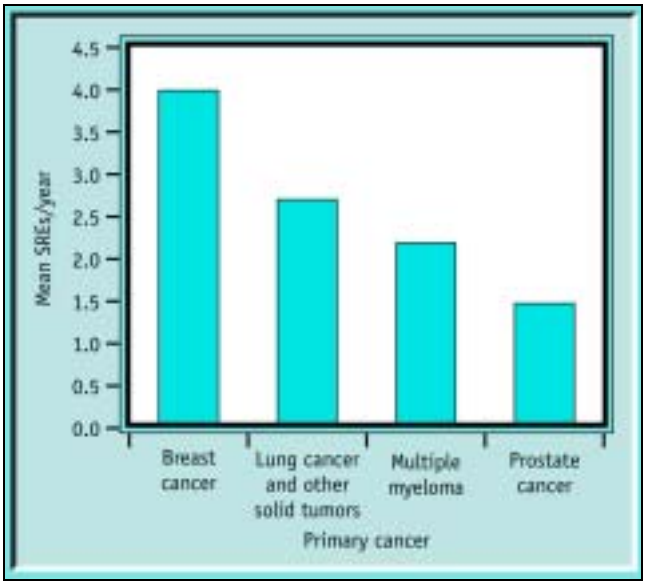

Figure 1. Incidence by primary malignancy of skeletal-related events (SREs) in patients with bone lesions. *From* Lipton [11]; with permission.

requirement for palliative radiotherapy, and sometimes hypercalcemia of malignancy (HCM). Use of SREs to quantify skeletal morbidity in patients with breast cancer or multiple myeloma is supported by the American Society of Clinical Oncology (ASCO) [14,15••]. Use of composite endpoints for drugs whose benefits are multifaceted (*eg*, bisphosphonates) was recently supported by Johnson *et al.* [16] of the US Food and Drug Administration (FDA).

- Although several other bisphosphonates have been investigated, only pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ) and zoledronic acid (Zometa; Novartis Pharmaceuticals, East Hanover, NJ) have received international approval for treating bone metastases in patients with breast cancer and are currently standards of care [15••].
- Ibandronate (both IV and oral) is approved in Europe for patients with bone metastases from breast cancer.
- Zoledronic acid is the only bisphosphonate to demonstrate efficacy in patients with osteoblastic lesions [17••] or bone metastases from solid tumors other than breast cancer, [18] and to demonstrate superiority over pamidronate in patients with breast cancer [19••].
- The ASCO guidelines recommend zoledronic acid or pamidronate for patients with breast cancer from first evidence of bone lesions until substantia decline in performance status [15••].
- The long-term efficacy results from phase III trials are summarized in Table 1 [4••,19••,20,21••]. The phase III clinical trial [19••,20] comparing pamidronate and zoledronic acid used conservative endpoints, including the proportion of patients with an SRE, median time to first SRE, and a statistically robust and multiple-event analysis found in the Andersen-Gill method [22] that incorporates the incidence and timing of all SREs during the course of the trial. In contrast, earlier trials of pamidronate and the recent trial of ibandronate used calculated rates of skeletal morbidity as their primary endpoint. The utility of skeletal morbidity rates to assess treatment benefits is limited by inter- and intrapatient variations [5•].
- As a class, IV bisphosphonates share a common safety profile [23].
- Possible acute phase (flu-like) symptoms following the first infusion.
- Possible effects on renal function.
- Administration guidelines should be closely followed to ensure patient safety and comfort.

Table 1. Long-term clinical trial results for nitrogen-containing intravenous bisphosphonates in patients with bone metastases secondary to breast cancer

Trial/endpoint	Key clinical comparison		*P* value
Rosen *et al.* [19••,21••]	*Zoledronic acid 4 mg (n=378*)*	*Pamidronate 90 mg (n=388*)*	
Patients with an SRE, %	46	49	NS
Median time to first SRE, months	NR	NR	NS*
Skeletal morbidity rate, SREs/*yr*	0.91	1.57	0.102
Multiple event analysis, hazard ratio	0.799	—	0.025
Lipton *et al.* [4••]	*Pamidronate 90 mg (n=367)*	*Placebo (n=384)*	
Patients with an SRE, %	53	68	< .001
Median time to first SRE, months	12.7	7	< .001
Skeletal morbidity rate, SREs/*yr*	2.5	4	< .001
Body *et al.* [20]	*Ibandronate 6 mg (n=154)*	*Placebo (n=158)*	
Patients with an SRE, %	51	62	0.052
Median time to first SRE, months	11.7	7.6	0.018
SMPR, intervals/year	1.19	1.48	0.004

*Treatment population and median time based on Rosen *et al.* [21••]. NR—not reported; NS—not significant; SMPR—skeletal-morbidity period rate; SRE—skeletal-related event.

- Serum creatinine should be monitored before any bisphosphonate infusion.
- Bisphosphonates should not be administered to patients who are dehydrated.

Pamidronate

The efficacy of pamidronate (90 mg through 2-hour infusion) every 3 to 4 weeks was established in 2 long-term, randomized, placebo-controlled trials in a total of 754 patients with stage IV breast cancer and osteolytic bone metastases [3,4••,24]. In patients receiving cytotoxic chemotherapy, pamidronate significantly reduced the percentage of patients with a skeletal complication after 2 years (50% vs 70% for placebo; $P \leq 0.001$) and extended the median time to first-skeletal complication by 7 months (13.9 vs 7.0 months for placebo; P 0.001) [24]. Similarly, in patients receiving hormonal therapy, pamidronate reduced the percentage of patients with a skeletal complication after 2 years (56% vs 67% for placebo; P=0.027) and significantly extended the median time to first skeletal complication (10.4 vs 6.9 months for placebo; P=0.049) [3]. The combined analysis of these two trials is shown in Table 1 [21••].

Pamidronate also provides long-term palliation of bone pain. In a 24-month analysis of clinical trial data in women with breast cancer receiving hormonal therapy or chemotherapy (n=754) [4••], patients treated with pamidronate experienced a significant decrease in mean pain score from baseline, compared with significantly increased mean pain scores in the placebo group (P=0.015). Compared with the placebo group, analgesic use in the pamidronate group was significantly lower ($P \leq 0.001$), and pamidronate-treated patients had less decrement in QoL and performance status at their last on-study assessments; although the differences did not reach significance (P=0.057 and P=0.088, respectively).

Based on these trials, pamidronate received international regulatory approval in 1996 and became the standard of care for the treatment of osteolytic bone metastases in patients with breast cancer.

Standard dosage Pamidronate (90 mg through 2-hour infusion every 3 to 4 weeks) is approved for the treatment of osteolytic bone lesions from multiple myeloma or breast cancer [25]. The optimal duration of therapy is not defined but the benefit has been demonstrated for up to 24 months of treatment [4••]. Current guidelines recommend that once initiated, treatment should be continued until the patient experiences notable serum creatinine increases or decreases in performance status [15••].

Contraindications Pamidronate is contraindicated during pregnancy and in patients with hypersensitivity to any bisphosphonate [25].

Main drug interactions No specific drug interaction information for humans is available.

Main side effects The most common adverse event associated with pamidronate and other nitrogen-containing bisphosphonates is an acute-phase reaction consisting of flu-like symptoms (*ie,* fever, nausea, and arthralgia or myalgia) [25]. In clinical trials in breast cancer, vomiting, anorexia, anemia, arthralgia, and myalgia were more common in patients receiving pamidronate than placebo [3]. In general, these transient side effects were mild to moderate in severity and were manageable with supportive care.

Special points Bisphosphonates have been associated with decreases in renal function, which are usually preceded by transient increases in serum creatinine. Therefore, serum creatinine should be measured before each dose of pamidronate is administered. The dose should be withheld for serum creatinine increases greater than or equals to 0.5 mg/dL in patients with normal baseline creatinine (≤1.4 mg/dL) or for serum creatinine increases greater than or equal to 1.0 mg/dL in patients with elevated baseline serum creatinine levels (≥1.4 mg/dL) [25].

Cost effectiveness The cost of pamidronate therapy is partially offset by the reduction in costs for managing skeletal morbidity because this treatment reduces the frequency of SREs in patients with osteolytic lesions [26]. However, in patients with breast cancer, the cost of administering pamidronate may exceed these cost savings. Nonetheless, bisphosphonates help to maintain performance status and QoL over time [27•] and are known to improve control of bone pain [28]. Therefore, the cost-effectiveness of long-term pamidronate therapy cannot be accurately be gauged.

Zoledronic acid

Based on its phase III efficacy and safety results, the regulatory approval of zoledronic acid (already indicated for HCM) was expanded to include the treatment of osteolytic lesions associated with multiple myeloma and bone metastases from a variety of solid tumors, including breast cancer, prostate cancer, lung cancer, and other solid tumors.

In the largest phase III clinical trial of bisphosphonates to date [19••,29•], patients with any bone metastases from breast cancer (*n*=1130) received either zoledronic acid (through 15-minute infusion) or pamidronate (through 2-hour infusion) in conjunction with standard antineoplastic therapy every 3 to 4 weeks for up to 2 years. The primary endpoint was the proportion of patients with an SRE [29•]. Notable increases in serum creatinine were strictly defined as increases greater than or equal to 0.5 mg/dL in patients whose baseline creatinine levels were normal (< 1.4 mg/dL), increases greater than or equal to 1.0 mg/dL in patients with elevated baseline serum creatinine levels, or any increase that resulted in doubling of the baseline value [19••,29•]. Creatinine increases were graded by the Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI).

The final 25-month analysis of patients with breast cancer in this trial is summarized in Table 1 [21••]. Zoledronic acid (4 mg) provided a significant additional 20% risk reduction of SREs compared with pamidronate (*P*=0.025) [19••]. Zoledronic acid was more effective than pamidronate at normalizing levels of bone resorption (reflected by urinary N-telopeptide), especially among the approximately 40% of patients with high levels at baseline [30].

In a 25-month subset analysis of breast cancer patients with greater than or equal to one osteolytic lesion, 4 mg zoledronic acid provided a significant 32% additional reduction in the risk of SREs (including HCM; *P*=0.003) and extended the median time to first SRE (including HCM) by 4.5 months (*P*=0.015) compared with pamidronate [31].

The proportion of patients with breast cancer with notable increases in serum creatinine was 9.4% for 4 mg zoledronic acid and 6.5% for pamidronate over the 25-month trial. No patients treated with 4 mg zoledronic acid through 15-minute infusion developed CTC serum creatinine of grade greater than 2, and only one patient treated with pamidronate had grade-4 serum creatinine. Zoledronic acid has also demonstrated superiority over pamidronate in the treatment of HCM [32•].

A recent single-arm study in 100 patients receiving hormonal therapy for breast cancer with bone metastases found that zoledronic acid (4 mg) significantly improved QoL (P=0.013) and decreased pain scores compared with baseline levels (worst pain, P=0.008; average pain, P=0.040) [33].

Standard dosage The approved dose of zoledronic acid is 4 mg through 15-minute infusion every 3 to 4 weeks [34]. Clinical benefit has been demonstrated over 24 months of treatment [19••], and current ASCO guidelines recommend that bisphosphonate therapy be continued as long as tolerated or until the patient has substantially decreased performance status [15••].

Contraindications All bisphosphonates are contraindicated during pregnancy or in patients with hypersensitivity to any bisphosphonate. Zoledronic acid is not recommended in patients with severe renal impairment (serum creatinine ≥ 3.0 mg/dL [265 mmol/L]) [34].

Main drug interactions No in vivo drug interaction studies have been performed. However, because of an increased risk of hypocalcemia, bisphosphonates should be administered with caution in patients being treated with agents known to lower serum calcium levels (*ie,* aminoglycosides or loop diuretics). Bisphosphonates should also be used with caution in patients who are receiving potentially nephrotoxic drugs.

Main side effects In clinical trials, adverse events reported with greater than or equal to 15% increased frequency in the zoledronic acid treatment arm compared with placebo were nausea, fatigue, pyrexia, vomiting, myalgia, and headache, [19,34] characteristic of transient bisphosphonate-associated acute-phase reactions. In the clinical trial comparing zoledronic acid with pamidronate, [19••] the safety profile was comparable between treatment groups. Generally, the side effects of zoledronic acid are transient, mild to moderate in severity, and can be managed with supportive care [23].

Special points Serum creatinine levels should be measured before each dose of zoledronic acid is administered. The creatinine criteria for withholding zoledronic acid are identical to those for pamidronate: treatment is withheld if serum creatinine increases by 0.5 mg/dL (if baseline serum creatinine was ≤1.4 mg/dL) or 1.0 mg/dL (if baseline serum creatinine was ≥ 1.4 mg/dL), or to double the baseline value; reinitiate zoledronic acid infusions when serum creatinine levels return to within 10% of baseline [34]. Serum creatinine should be monitored during therapy and specific guidelines have been published [23].

Cost effectiveness The administration costs (both monetary and in terms of resource utilization) of zoledronic acid compared with those of pamidronate were assessed in a microcosting analysis in patients with bone lesions from multiple myeloma or breast cancer [35]. This study did not analyze the relative costs of the medications themselves, but revealed that the per-patient costs associated with each infusion was 6% lower for patients receiving zoledronic acid compared with pamidronate. The increased cost for the pamidronate infusion was attributed to the longer infusion time, which occupied an additional 1.8 hours of nurse monitoring time per infusion. Similar to pamidronate, the cost of zoledronic acid should be at least partially offset by decreased costs associated with skeletal complications, but this has not been formally studied.

Ibandronate

Ibandronate (Bondronat; Roche, Basel, Switzerland) has received approval in the European Union as an IV therapy for HCM and, more recently, for the treatment of bone metastases secondary to breast cancer, but is not approved for any indication in the United States [36]. These approvals were based on placebo-controlled trials; ibandronate has not been compared with an active bisphosphonate. Therefore, the clinical activity of ibandronate compared with either pamidronate or zoledronic acid is not known.

A phase III, multicenter, parallel-group study compared IV ibandronate (6 mg through 1- to 2-hour infusion or 2 mg through bolus injection) with placebo every 3 to 4 weeks in women with breast cancer metastatic to bone (n=466) [20]. This trial included patients receiving concomitant hormonal therapy (n=283), chemotherapy (n=110), or no active anticancer therapy (n=69).

The primary efficacy endpoint was the skeletal morbidity period rate (SMPR), which is the number of 12-week periods with a bone complication divided by the study time.

Treatment with 6 mg ibandronate significantly reduced the mean SMPR (1.19 for 6 mg ibandronate vs 1.48 for placebo; *P*=0.004) and significantly prolonged the median time to first new bone event (50.6 weeks vs 33.1 weeks for placebo; *P*=0.018), whereas the 2-mg ibandronate dose was not effective. six mg ibandronate reduced the proportion of patients with a bone complication (51% for 6 mg ibandronate vs 62% for placebo; *P*=0.052) [20].

Clinically relevant serum creatinine elevation was reported in four (2.6%) patients treated with 6 mg ibandronate, one (0.7%) patient treated with 2 mg ibandronate, and two (1.3%) patients receiving placebo [20]. The incidence of severe (CTC grade 3 or 4) renal events was not reported.

In a 3-month study comparing serum creatinine levels in patients treated with 1-hour infusions of 6 mg ibandronate (*n*=28) or placebo (*n*=23) each month, no significant differences were reported, and no patients developed CTC grade greater than or equal to 1 serum creatinine increases [37]. However, this was a small study that enrolled only patients at a single site and with normal baseline serum creatinine, and bisphosphonate effects on renal function are infrequent during short-term therapy.

Standard dosage In countries where IV ibandronate is approved, the approved dose is 2 to 6 mg through 2-hour infusion for HCM or 6 mg through 1-hour infusion every 3 to 4 weeks for bone metastases [20,36].

Contraindications Ibandronate is contraindicated during pregnancy and in patients with serum creatinine greater than 5 mg/dL (442 μmol/L) [36]. Ibandronate should not be administered to patients with hypersensitivity to ibandronate or its excipients, and should be used cautiously in patients who have hypersensitivity to any other bisphosphonates [36].

Main drug interactions Patients who are receiving aminoglycosides should be carefully monitored during ibandronate therapy, as both agents are associated with hypocalcemia.

Main side effects Detailed safety information and incidence of grade 3 or 4 serum creatinine from phase III testing have not been published. However, the incidence of serum creatinine level increases greater than 300 μmol/L was 2-fold higher in the 6-mg ibandronate group than in the placebo group. Similar to trials of other nitrogen-containing bisphosphonates in this patient population, most patients experienced greater than or equal to 1 adverse event, the majority of which were related to disease progression [20]. Consistent with acute-phase reactions, flu-like symptoms and arthralgia were more common in patients treated with ibandronate compared with placebo.

Special points No clinical trial has compared ibandronate with pamidronate or zoledronic acid in patients with bone metastases. The full safety data from the ibandronate trials have not been published, and there has been limited clinical experience with ibandronate in treating bone metastases outside the clinical trial setting. Therefore, risk factors for adverse events have not been fully evaluated.

Cost effectiveness No data are currently available to assess treatment costs with ibandronate.

Emerging therapies

Prevention of cancer treatment-induced bone loss

- An emerging area of concern for oncologists is that of cancer treatment-induced bone loss (CTIBL). Even before developing bone metastases, patients receiving therapy for breast cancer suffer cumulative effects from CTIBL, often experiencing significant decreases in bone mineral density. Preventing CTIBL may maintain bone health and lower rates of skeletal morbidity when patients develop bone metastases, though further studies are necessary. Current treatment options for CTIBL include estrogen receptor modulators, dietary calcium and vitamin D supplements, calcitonin, and oral nitrogen, containing bisphosphonates.

- Based on promising results in patients receiving goserelin-based therapy [38], two international clinical trials are underway to investigate the safety and efficacy of IV zoledronic acid for the prevention of CTIBL during adjuvant aromatase inhibitor therapy.

Prevention of bone metastases

- Indirect evidence from preclinical models suggests that bisphosphonates may delay the development of new bone metastases. This is supported by delays in bone lesion progression during long-term bisphosphonate therapy [4••,39–43], and the lower incidence of bone metastases in patients treated with clodronate for early stage breast cancer in some trials [41–43]. Zoledronic acid has demonstrated superior antitumor effects compared with other bisphosphonates in preclinical models [12,44].
- The adjuvant therapy for breast cancer (AZURE) study is comparing the effects of zoledronic acid with those of placebo on disease-free survival in 3400 patients with breast cancer receiving standard adjuvant therapies.
- A large, randomized trial is planned by the Southwest Oncology Group (SWOG) to compare the benefits of oral clodronate, oral ibandronate, and IV zoledronic acid for 3 years as an adjunct to standard adjuvant therapy in women with breast cancer.
- The AZURE and SWOG studies will help to define the emerging role of bisphosphonates during adjuvant therapy and determine if bisphosphonates can improve outcomes in patients with early stage breast cancer. The effects of early therapy on the development of bone metastases will be of particular interest.

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