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Breast Cancer (EA Comen, Section Editor)

Role of Bisphosphonates in Breast Cancer Therapy

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Opinion statement

Bisphosphonates are utilized routinely in breast cancer. In metastatic disease with bone involvement, bisphosphonates prevent or delay skeletal-related events and can improve pain control. Different agents have shown benefit compared with placebo or no treatment. While in unselected patients, comparison between zoledronic acid and pamidronate did not show a significant difference, exploratory analyses showed that in patients with osteolytic lesions or hypercalcemia, zoledronic acid is superior to pamidronate. De-escalating treatment with zoledronic acid from every 4 to every 12 weeks has been shown to provide similar control of skeletal morbidity and may result in less toxicity and reduced cost. While available data support bisphosphonate treatment for 2 years in metastatic disease, typical treatment duration is influenced by performance status with treatment discontinued only once patients are not well enough to continue receiving systemic therapy or developed treatment-related adverse events. In early-stage breast cancer, individual trials of adjuvant bisphosphonates have reported inconsistent results. However, the Early Breast Cancer Trialists' Collaborative Group showed that bisphosphonates significantly reduce distant recurrence, bone recurrence, and breast cancer mortality, an effect observed in postmenopausal women only. The relative benefit of bisphosphonates was not influenced by receptor status, tumor grade, nodal involvement, or administration of adjuvant chemotherapy. Current guidelines support consideration of adjuvant zoledronic acid or oral clodronate for 3–5 years in postmenopausal women with early-stage disease. Although bisphosphonates are tolerated well, serious adverse events, including osteonecrosis of the jaw and renal impairment, can occur, especially for higher dose density schedules utilized in metastatic disease. Decision to

include bisphosphonates in the treatment plan should be based on the anticipated absolute benefit and potential for adverse effects. In some patients with both early-stage and metastatic disease, omission of bisphosphonates is reasonable as the potential benefit from this treatment is not likely to outweigh its risks.

Introduction

Bone is the most common site of metastasis in patients with breast cancer. About 65–75% of patients with advanced disease develop bone metastases [1]. Bisphosphonates are bone-modifying agents and have an important role in the treatment of women with both early-stage and metastatic breast cancer.

Bisphosphonates inhibit osteoclastic bone resorption by attaching to hydroxyapatite binding sites on bony surfaces, especially surfaces undergoing active resorption. This results in the inhibition of enzymes that utilize pyrophosphate [2]. Bisphosphonates also reduce osteoclast activity by decreasing osteoclast progenitor development and recruitment and by promoting osteoclast apoptosis [3]. The effect of this activity has resulted in bisphosphonates becoming a standard part of the armamentarium for the treatment of breast cancer. Several bisphosphonates have been investigated in breast cancer. A summary of the dosage, route of administration, efficacy, and significant adverse effects from the major studies in metastatic and early-stage disease are shown in Tables 1 and 2, respectively. In this manuscript, we review the current data on bisphosphonate treatment in patients with metastatic and early-stage breast cancer.

Metastatic disease

Bone metastases can result in skeletal-related events (SREs), which are a clinically defined group of events comprising pathologic fracture, spinal cord compression, hypercalcemia, and pain requiring radiotherapy or surgery to bone. As SREs have a significant impact on patients' morbidity and quality of life, reducing the incidence of SREs is valuable. In breast cancer patients with bone metastases, the addition of bisphosphonates to standard treatment is associated with a statistically significant 15% reduction in the risk for SREs as well as a significantly delay in time to SRE, and an improvement in bone pain [26••, 27]. However, individual studies of bisphosphonates have not shown that reducing skeletal morbidity results in improvements in overall quality of life, progression-free survival (PFS), or overall survival (OS) compared with placebo [26••, 28].

The first evidence supporting the benefit of adding bisphosphonate to standard treatment emerged over two decades ago with placebo-controlled, randomized trials showing that treatment with pamidronate significantly reduced the incidence of SREs and delayed the onset of SREs [4, 5]. Pamidronate was given for 2 years as a 2-h infusion every 3–4 weeks. Subsequently, several studies evaluated the efficacy of zoledronic acid, a more potent bisphosphonate that can be administered safely over 15 min [29]. Head-to-head comparisons of zoledronic acid and pamidronate did not show a significant effect on SRE incidence overall [9]; however, zoledronic acid seemed superior to pamidronate in post hoc subgroup

Table 1. Summary of studies evaluating bisphosphonates in metastatic disease

Study	Comparison	Patients	Major results (investigational vs. control)	Serious toxicity (investigational vs. control)
Hortobagy et al. Protocol 19 Aredia [4]	IV pamidronate 90 mg vs. placebo q 3–4 weeks for 2 years	382 patients with metastatic breast cancer and lytic bone lesion	- Median duration of treatment 13 vs. 10.2 months - 2-year SRE 50% vs. 70%, $p < 0.001$ - OR for SRE 2.3, 95% CI 1.5–3.5 - Median time for first SRE 13.9 vs. 7 months, $p < 0.001$ - Median OS 14.8 vs. 14.0 months, $p = 0.82$ - No significant difference in quality of life - Significant worsening in ECOG PS with placebo	- Myalgias, arthralgias, and influenza-like symptoms were slightly more common in the pamidronate group (numbers are not available)
Theriault et al. Protocol 18 Aredia Breast Cancer Study Group [5]	IV pamidronate 90 mg vs. placebo q 4 weeks for 2 years	372 patients with metastatic breast cancer and lytic bone lesion	- Median duration on treatment 17.4 vs. 14.6 months - 2-year SRE 56% vs. 67%, $p = 0.049$ - OR for SRE 1.6, 95% CI 1.1–2.5 - Median time for first SRE 10.4 vs. 6.9 months, $p = 0.049$ - Worsening pain score with placebo ($p = 0.007$) - Median OS 23.2 vs. 23.5 months, $p = 0.685$	- Injection site reactions 6% vs. 0.5% - Chemotherapy-associated leukopenia 9% vs. 4% - Serious AEs 2 vs. 1 events
Paterson et al. [6]	Oral clodronate 1,600 mg daily vs. placebo for 18 months	173 patients with metastatic breast cancer	- Combined rate of all morbid skeletal events 218.6 vs. 304.8 per 100 patient-years, $p < 0.001$ - Hypercalcemic episodes 28 vs. 52, $p < 0.01$ - Incidence of vertebral fractures 84 vs. 124 per 100 patient-years, $p < 0.025$ - NS OS difference	- Treatment discontinuation 29 vs. 32 patients - No difference in all side effects that were assessed
Body et al. [7]	Oral ibandronate 50 mg vs. placebo for up to 96 weeks (additional arm treated with ibandronate 20 mg not included in the analysis)	564 patients with metastatic breast cancer Pooled analysis from 2 randomized trials	- Complete 96 weeks of treatment 42% vs. 38% - Mean SMRP 0.99 vs. 1.15, $p = 0.041$ - Number of events per patients 1.15 vs. 1.85, $p = 0.008$ - Risk reduction for SRE: HR = 0.62, 95% CI 0.48–0.79, $p < 0.001$ - Death 20% vs. 15%	- Any AEs 94.4% vs. 95.3% - Drug-related AEs 26.6% vs. 17.7% - Serious drug-related AEs 1% vs. 1.4% - Hypocalcemia 9.4% vs. 5.1% - Esophagitis 2.1% vs. 0.7% - Renal AEs 5.2% vs. 4.7%
	IV zoledronic acid 4 vs. IV	1,648 patients with metastatic		- Renal and urinary AE 10.9% vs. 6.7%

Table 1. (Continued)

Study	Comparison	Patients	Major results (investigational vs. control)	Serious toxicity (investigational vs. control)
Rosen et al. [8, 9][1]	zoledronic acid 4/8 mg vs. IV pamidronate 90 mg for 12 months	breast carcinoma or multiple myeloma 1130 patients with metastatic breast cancer	- SREs at 13 months (excluding hypercalcemia) 44% vs. 46% vs. 46% - Skeletal morbidity rate (including hypercalcemia) 1.13 vs. 1.08 vs. 1.4 events/year (not significant) - NS difference in ECOG PS deterioration - NS difference in pain score - No significant difference in median time to disease progression and in median OS Analysis for breast cancer patients [8] - SREs at 13 months for all breast cancer patients 43% vs. 45% vs. 45% - SREs at 13 months for patients with lytic lesion 48% vs. 51% vs. 58% (p = 0.058 for the difference between zoledronic acid compared with pamidronate) - SREs at 13 months for patients without lytic lesion 38% vs. 39% vs. 36% (NS) - Time for first SRE for patients with lytic lesion 310 vs. 174 days, p = 0.013 (zoledronic acid 4 mg vs. pamidronate, respectively) - Time for first SRE for patient without lytic lesion: NS difference	- Bone pain 49% vs. 59%
Major et al. [10][2]	IV zoledronic acid 4 vs. IV zoledronic acid 8 mg vs. IV pamidronate 90 mg When refractory to initial therapy/relapsed up to 56 days after first dose re-treatment with zoledronic acid 8 mg	275 patients with cancer and severe hypercalcemia, 18.5% were with breast cancer	- Adequate decrease in hypercalcemia[3] in 10 days 88.4% (p = 0.002) vs. 86.7% (p = 0.015) vs. 69.7% - Median time to relapse 30 (p = 0.001) vs. 40 (p = 0.007) vs. 17 days	- Any adverse event 94.2% vs. 95.9% vs. 92.2% - Elevate serum creatinine, grades 3–4 2.3% vs. 5.2% vs. 4% - Fever 44.2% vs. 34.7% vs. 33%
Barrett-Lee et al.	Oral ibandronate 50 mg vs. IV		- Median time on treatment 75 weeks for both arms	- Any AEs, all grades 96% vs. 96%

Table 1. (Continued)

Study	Comparison	Patients	Major results (investigational vs. control)	Serious toxicity (investigational vs. control)
ZICE study [11]	zoledronic acid 4 mg q 3–4 weeks for 96 weeks	1401 patients with metastatic breast cancer	- SREs 42% vs. 41% - Rate ratio for SRE 1.15, 95% CI 0.97–1.62 - Median time for SRE 97 vs. 99 weeks, HR = 1.03, 95% CI 0.87–1.23 - Median OS 111 vs. 113 weeks	- Dyspepsia 35% vs. 25% - Hypocalcemia 11% vs. 11% - Renal impairment 24% vs. 32% - ONJ 5 vs. 9 events
Stopeck et al. [12]	SC denosumab 120 mg and IV placebo vs. IV zoledronic acid 4 mg and SC placebo q 4 weeks	2046 patients with metastatic breast cancer	- Delayed time to first SRE: HR = 0.82, 95% CI 0.71–0.95, $p < 0.001$ - Risk of developing multiple SREs: HR = 0.77, 95% CI 0.66–0.89, $p = 0.001$ - OS: HR = 0.95, 95% CI 0.81–1.11, $p = 0.49$ - Disease progression: HR = 1.00, 95% CI 0.89–1.11, $p = 0.93$ - HRQoL: in the denosumab group, 10% more patients had a clinically meaningful improvement in HRQoL [13]	- Adverse events leading to treatment discontinuation 9.6% vs. 12.3% - Serious adverse events 44.4% vs. 46.5% - Pyrexia 16.7% vs. 24.4% - Bone pain 18.2% vs. 23.5% - Adverse events potentially associated with renal toxicity 4.9% vs. 8.5% - ONJ 2% vs. 1.4%

[1]Amendment during the study changed the treatment in the arm of 8 mg zoledronic acid to 4 mg in light of concern from renal safety; then, the arm name was changed to 4/8 mg
[2]Combined results from 2 randomized trials
[3]Adequate response: corrected serum calcium was ≤ 2.70 mmol/L (10.8 mg/dL). *p* values are the comparison to the pamidronate arm
CI, confidence interval; *ECOG*, Eastern Cooperative Oncology Group; *HRQoL*, health-related quality of life; *IV*, intravenous; *NS*, not significant; *OR*, odds ratio; *PS*, performance status; *SC*, subcutaneous; *SMRP*, skeletal morbidity period rate; *SRE*, skeletal-related event

analyses such as in patients with malignancy-associated hypercalcemia [10] and in those with at least one osteolytic bone lesion (i.e., excluding those with exclusively sclerotic disease) [8].

Treatment with oral clodronate and ibandronate also showed a significant reduction in SREs compared with placebo [6, 7, 30], suggesting oral treatment is an alternative to infusional bisphosphonates. However, the head-to-head ZICE trial has failed to show non-inferiority of ibandronate compared with zoledronic acid (risk ratio for SRE 1.15, 95% CI 0.97–1.36, exceeding the predefined upper CI margin of 1.08) [11]. Of note, ibandronate was associated with significantly reduced risk of nephrotoxicity and non-significantly fewer osteonecrosis of jaw (ONJ) events [11].

Data on the benefit of bisphosphonate beyond 2 years are scarce. As such, the optimal duration with bisphosphonates for metastatic disease remains unclear. The American Society of Clinical Oncology (ASCO) guidelines recommend that bisphosphonates should be given until there is a substantial decline in the patient's general performance status [31].

Table 2. Summary of studies evaluating bisphosphonates in early breast cancer

Study	Comparison	Patients	Major results (investigational vs. control)	Serious toxicity (investigational vs. control)
Diel et al [14,15][1]	Oral clodronate 1600 mg daily for 2 years vs. Observation	302 patients with tumor cells in the bone marrow Postmenopausal: 63%	-Distant metastases: 38.9% vs. 39.3% (p=0.816) -Distant metastases: 23.6% vs. 26.2% (p=0.77) -Deaths: 20.4% vs. 40.7% (p=0.049)	NR
Powles et al. [16]	Oral clodronate 1600 mg daily for 2 years vs. placebo	1069 patients Postmenopausal: 51%	-Risk for bone metastases: 9.6% vs. 13.5%, HR = 0.69, *p*=0.043 -Deaths: 18.5% vs. 23.9%, HR=0.77, *p*=0.048	-Treatment discontinues for adverse events: 13% vs. 11% -Diarrhea: 19.9% vs. 10%, P<0.05 -No events of ONJ
Paterson et al. NSABP B34 [17]	Oral clodronate 1600 mg daily for 3 years vs. placebo	3311 patients Age ≥ 50: 65%	-DFS: HR=0.91, 95% CI 0.78–1.07, p=0.27. -OS: HR=0.84, 95% CI 0.67–1.05, p=0.13 -Recurrence-free interval: HR=0.83, 95% CI 0.67–1.04; p=0.10 -Bone metastasis-free interval: HR=0.77, 95% CI 0.55–1.07, p=0.12 *For age 50* ≥ Recurrence-free interval: HR=0.75, 95% CI 0.57–0.99, p=0.045 -Bone metastasis-free interval: HR=0·62, 0.40–0.95, p=0.027. OS: HR=0.80, 0.61–1.04, p=0.094.	-Completed 3 years treatment: 56% vs. 60%, p=0.004 -ONJ: 1 event vs. 0 -Diarrhea grade ≥ 3: 28 vs. 10 events -Increased creatinine grade ≥ 3: 4 vs. 0 events.
von Minckwitz et al, GAIN study [18]	Oral ibandronate 50 mg daily for 2 years vs. observation, randomization 2:1	2994 patients with nodal involvement Postmenopausal: 52%	-DFS: HR=0.95, 95% CI 0.77-1.16, p = 0.589 -OS: HR=1.04, 95% CI=0.76-1.42, p = 0.803 -Bone metastases: 31% vs. 38%	-Any AEs (any grade): 21.8% vs. 15.4%, p<0.001 -ONJ: 2 events in the ibandronate arm -Gastrointestinal AEs: 5.7% vs. 3.4%, p=0.007

Table 2. (Continued)

Study	Comparison	Patients	Major results (investigational vs. control)	Serious toxicity (investigational vs. control)
				-Hepatobiliary AEs: 1.2% vs. 0.3%, p=0.013
Kristensen et al [19]	Oral pamidronate 150 mg BID daily for 4 years vs. observation	953 patients Postmenopausal: 33%	-Recurrence in bone: HR=1.03, 95% CI 0.75–1.40, p=0.86 -No effect on OS	-Similar incidence of: nausea, vomiting, stomatitis and abdominal pain
Coleman et al, AZURE (BIG 01/04) [20]	IV zoledronic acid 4 mg q 3–4 weeks * 6 → q 3 months * 8 → q 6 months * 5 vs. observation	3360 patients > 5 years since menopause: 31%	-DFS: HR=0.94, 95% CI 0.82–1.06, p=0.30 -OS: HR=0.93, 0.81–1.08, p=0.37 -Bone metastases as 1st recurrence: HR=0.78, 95% CI 0.63–0.96, p=0.02 -Incidence of bone recurrence at any time: HR=0.81, 0.68–0.97, p=0.022 *Subgroup analysis for women >5 years since menopause:* -Non-bone first IDFS event: HR=0.77, 95% CI 0·61–0·97 -Bone first IDFS event: HR=0.79, 95% CI 0.53–1.17	-Confirmed ONJ 26[2] (1.54%) vs. 0 events -Serious AEs: 580 (34%) vs. 509 (31%)
Gnant et al, ABCSG 12 [21]	IV zoledronic acid 4 mg q 6 months * 6 vs. observation	1803 patients with hormone receptor positive disease Postmenopausal: 0%, but all women were treated with ovarian function suppression	-DFS: HR=0.77, 95% CI 0.60–0.99, p=0.042. -OS: HR=0.66, 95% CI 0.43–1.02, p=0.064 -Bone recurrence: HR=0.76, 95% CI 0.46–1.25	-ONJ: no confirmed cases. -Renal failure: no events. -Serious AEs: 30% vs 27%
von Minckwitz et al, NaTaN study [22]	IV zoledronic acid 4 mg q 3–4 weeks * 6 → q 3 months * 8 → q 6 months * 5 vs. observation Postmenopausal 70%	693 patients who did not have pCR after neoadjuvant chemotherapy with at least 4 cycles, comprising taxane and anthracycline	-DFS: HR=0.96, 95% CI 0.71–1.30, p=0.789 -OS: HR=1.19, 95% CI 0.79–1.79, p=0.408 - Bone metastasis-free survival: HR=1.08, 95% CI 0.76–1.54, p = 0.658 *Menopausal status did not affect the results*	-Any AE, all grades: 86.4% vs. 75%, p=0.002, -Any AE, grade 3-5: 29% vs. 21%, p=0.032

Table 2. (Continued)

Study	Comparison	Patients	Major results (investigational vs. control)	Serious toxicity (investigational vs. control)
				-Renal and urinary AE: 3.1% vs. 1.7%, p=0.372 -Fever: 12.3% vs. 0.4%, p<0.001 -Bone pain: 27.2% vs. 17%, p=0.01 -ONJ: 5 vs 0 events
Jani et al, SUCCESS A study [23]	IV zoledronic acid 4 mg q 3 months for 2 years→ zoledronic acid q 6 months for 3 years vs. IV zoledronic acid 4 mg q 3 months for 2 years	2987 patients previously treated with chemotherapy (FEC-D ±G) Postmenopausal: 58%	-DFS: HR=0.97, 95% CI 0.75-1.25, p=0.81 -OS: HR=0.98, 95% CI 0.67-1.42, p=0.90 *Menopausal status did not affect the results of DFS and OS* -Bone recurrences: 25 vs. 28 events, p=0.427	-Any AE, all grades: 46.2% vs. 27.2%, p<0.001 -Any AE, grade 3-5: 7.6% vs. 5.1%, p=0.006 -Bone pain: 8.3% vs. 3.7% -Elevated SGPT: 2.5% vs 0.7% -ONJ: 11 vs 5 events
SWOG S0307 study [24,25]	3 years treatment with: oral clodronate 1600 mg daily vs. oral ibandronate 50 mg daily vs. IV zoledronic acid 4 mg (IV monthly * 6→q 3 months for 2.5 years)	6,097 patients Postmenopausal or age>50: 58%	-5-year DFS: 88% vs. 87% vs. 87%, p = 0.71 -5-year OS: 93% in all arms	-ONJ: 0.3% vs. 0.6% vs. 1.2%

[1]Results from the updated publication.
[2]There were additional 7 unconfirmed events of ONJ.
ABCSG=Austrian Breast and Colorectal Cancer Study Group; CI= confidence interval; DFS= disease free survival; FEC-D: 5-FU, epirubicin, cyclophosphamide and docetaxel; G= gemcitabine; IDFS= invasive disease-free survival; GAIN= German Adjuvant Intergroup Node-Positive; HR=hazard ratio; NR= not reported; NSABP= National Surgical Adjuvant Breast and Bowel Project; ONJ= osteonecrosis of jaw; OS= overall survival; SWOG= Southwest Oncology Group

Recently, there has been increasing interest in de-escalating the dose density of zoledronic acid. Several randomized trials have shown non-inferiority of zoledronic acid every 12 weeks compared with infusion every 4 weeks [32–34], suggesting de-escalated zoledronic acid administration might be a preferred option in metastatic disease, as it is more convenient and may result in less toxicity and reduced cost.

Denosumab is a bone-modifying agent that can be used instead of bisphosphonates in women with metastatic breast cancer. It is a fully humanized monoclonal antibody which inhibits nuclear factor kappa-B ligand (RANKL). The toxicity profile of denosumab is similar to bisphosphonates with similar risk for ONJ, but with a higher risk for

hypocalcemia [35]. In contrast to zoledronic acid, denosumab has minimal nephrotoxicity and can be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) with close monitoring of calcium levels [36]. In metastatic disease, subcutaneous denosumab dosed at 120 mg every 4 weeks has shown to delay the first SRE compared with zoledronic acid; however, as seen in the placebo-controlled bisphosphonate trials, no effect on PFS or OS was observed [12, 13]. The benefit of denosumab in terms of SRE delay should be balanced by its significantly greater cost compared with that of bisphosphonates. A recent cost-effectiveness analysis showed that zoledronic acid every 12 weeks is more cost-effective than denosumab [37]. Additionally, international practice guidelines have not stated a preference for either denosumab or bisphosphonates, reflecting their similar efficacy and toxicity profile in unselected patients [38–40].

While the primary endpoints that were used in the different bisphosphonate studies were SRE-based primary outcomes and results of trials reported significantly better outcomes with bisphosphonates, this effect did not translate to an improvement in either PFS or OS or a consistent effect on overall quality of life. SREs are a composite measure of skeletal morbidity. The most common SRE is bone pain requiring radiation, accounting for about two-thirds of all SREs. More serious SREs such as spinal cord compression that can lead to paralysis are less common [41]. As most SREs are bone pain requiring radiation, the lack of impact of bisphosphonates on quality of life could be explained by the fact that radiation for bone pain is a very effective treatment without significant toxicity, and the avoidance of palliative radiation with bisphosphonates is less likely to impact quality of life.

Bisphosphonates have a relatively modest toxicity profile, however may result in toxicity, and for intravenous bisphosphonates, the need to attend infusion clinics for treatment also increases patients' visits and costs. As the main objective of treatment for metastatic disease is to improve either the duration of survival or quality of life, it is uncertain to what degree bisphosphonates aid in this setting. Re-thinking the primary outcome measures of trials assessing the efficacy of bone-targeted agents is warranted, and inclusion of measures of quality of life or survival seems desirable [28]. Omission of bone-targeted treatment in asymptomatic patients with low burden of metastatic bone disease is a reasonable approach, along with adequate surveillance.

Early-stage disease

Disseminated tumor cells in the bone marrow can be identified in about a quarter of patients with early-stage breast cancer, and the presence of these cells is associated with adverse prognosis including an increased risk for recurrence [42]. The bone and bone marrow microenvironment have an important role in the development of bone metastases. Circulating tumor cells are attracted to the bone marrow microenvironment and bind to the osteoblastic niche by displacing hemopoietic stem cells [43]. These cells can escape the effect of adjuvant systemic therapy and subsequently proliferate to develop into metastatic disease [44]. The osteoblastic niche is maintained by bone turnover which

in turn is dependent on the balance between osteogenesis and bone resorption. Many cytokines and hormones are involved in the regulation of bone turnover including sex steroids [45, 46]. Estrogen-deficient states result in increased bone resorption. During this process, growth factors are released into the bone microenvironment, which is hypothesized to create an environment conducive for metastasis and tumor cell proliferation [47, 48]. Inhibition of osteoclast-driven bone resorption using bisphosphonates is thought to reduce this growth factor cascade, thereby reducing the risk of bone metastasis [49]. This mechanism together with the known benefit of bisphosphonate on bones in metastatic disease has been the justification for the study of bisphosphonates in the early-stage breast cancer setting. As low estrogen states such as postmenopause or the use of ovarian function suppression are associated with accelerated bone resorption, the effect of bisphosphonates is expected to be most marked in these settings.

During the last three decades, many trials of adjuvant bisphosphonates have been completed with inconsistent results. Diel et al. showed that in patients with early-stage disease with at least one tumor cell detected in the bone marrow, 2 years of oral clodronate reduced the incidence of metastatic disease, including both bone and visceral metastases. A significant improvement in OS compared with no treatment was also observed [14]. Interestingly, in the updated publication, the improvement in OS remained significant, while the reduction in the development of metastatic disease did not [15]. Another placebo-controlled clodronate study showed a significant reduction in bone metastases, but without a significant effect on OS [16]. In contrast, the larger NSABP-B34 study did not show any improvement in outcome with 3 years of adjuvant clodronate [17]. However, in a prespecified subgroup analysis, improvements in recurrence-free survival (which did not include non-breast cancer death), bone metastasis–free survival, and non-bone metastasis–free interval were noted for women older than 50, implying some breast cancer–specific benefits from clodronate in postmenopausal women [17].

Zoledronic acid has also been assessed in several randomized trials. The AZURE study was the largest adjuvant study comparing zoledronic acid with no treatment [19]. Treatment with zoledronic acid continued for 5 years and utilized a dose-dense schedule with the first 6 doses given every 3–4 weeks, followed by 2 years of treatment at 3-month interval and the remaining 2.5 years at 6-month interval. Zoledronic acid significantly reduced the incidence of bone metastases, though neither disease-free survival (DFS) nor OS was improved [19]. Similar to the NSABP-B34 study, a prespecified subgroup analysis in postmenopausal women showed that zoledronic acid was associated with significantly improved invasive DFS [19]. Similar data were reported in the ABCSG-12 study which enrolled premenopausal women who were all rendered menopausal with gonadotropin-releasing hormone agonists [21]. Compared with no treatment, zoledronic acid given every 6 months for 3 years improved DFS significantly [21]. In contrast, in the NaTaN study, an open-label study that included only high-risk patients who did not achieve a pathological complete response after neoadjuvant chemotherapy, outcomes were comparable in the bisphosphonate and observation group and menopausal status did not have significant impact on the results [22]. Of note, in the NaTaN study, duration and intensity of zoledronic acid were similar to the AZURE study, but enrollment was allowed up to 3 years from surgery (defined as the time of

axillary dissection). This may have resulted in immortal time bias as some patients would have had to be free of recurrence at the 3-year time point, potentially explaining the differences seen in the NaTaN trial and other adjuvant bisphosphonate studies. Other oral bisphosphonates such as oral pamidronate and ibandronate have failed to show advantage in the adjuvant setting [18, 19].

The Southwest Oncology Group (SWOG) S0307 study is the only large randomized study comparing different bisphosphonates (clodronate, ibandronate, and zoledronic acid) [24, 25]. Results presented in abstract form showed no statistically significant difference in 5-year DFS (which ranged between 86 and 87%) or in OS (which was 93% for all 3 arms). ONJ was uncommon, but there were significantly more events with zoledronic acid, compared with clodronate and ibandronate (1.2% vs. 0.3% and 0.7%, respectively, $p = 0.003$) [24].

In 2015, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported on a meta-analysis comprising more than 18000 patients from 26 studies comparing 2–5 years of adjuvant bisphosphonate with placebo or no treatment [48]. A prespecified subgroup analysis by menopausal status (postmenopausal status included natural and induced menopause) was also performed. Among all patients, there was a significant reduction in distant recurrence (rate ratio [RR] 0.92, 0.85–0.99, $p = 0.03$) as well as a similar effect on breast cancer mortality (RR = 0.91, 0.83–0.99, $p = 0.04$). However, subgroup analysis by menopausal status showed that postmenopausal women had higher magnitude reductions in distant recurrence (RR = 0.82, 0.74–0.92, $p = 0.0003$), bone recurrence (RR = 0.72, 0.60–0.86, $p = 0.0002$), and breast cancer mortality (RR = 0.82, 0.73–0.93, $p = 0.002$). No such effect was observed in premenopausal women. This benefit from bisphosphonates in postmenopausal women was independent of bisphosphonate class, scheduling, estrogen receptor expression, nodal status, tumor grade, or concomitant chemotherapy. The EBCTCG analysis was unable to assess the incidence of osteonecrosis of the jaw [48], but based on individual studies' reports, it ranged from under 1% with oral bisphosphonates [17, 18] or 6 monthly zoledronic acid [21] to up to 2% with more intensive zoledronic acid schedules [49].

Following the publication of the EBCTCG meta-analysis, several groups including a new, joint clinical practice guideline from Cancer Care Ontario (CCO) and the ASCO [38], the St. Gallen International Breast Cancer Consensus [50], and European panel committee [51] concluded that adjuvant zoledronic acid or oral clodronate should be considered in postmenopausal women with early-stage breast cancer. Individual decision should be made based on the risk of recurrence, patient age, comorbidities, and the risk of developing renal impairment or ONJ. As the risk of toxicity might outweigh the estimated small benefit in patients with very low-risk breast cancer, omitting adjuvant bisphosphonate in this population is reasonable.

The variability in the duration of adjuvant bisphosphonates in the various trials leads to uncertainty about the optimal duration of treatment. According to the joint CCO and ASCO guidelines, adjuvant bisphosphonates should comprise zoledronic acid every 6 months for 3

to 5 years or clodronate daily for 2 to 3 years [38]. The SUCCESS A study compared 2 and 5 of adjuvant zoledronic acid, with treatment given at 3-month interval during the first 2 years [23]. The duration of treatment had no effect on bone recurrences, DFS, or OS. Additionally, menopausal status had no impact on results. Shorter treatment was associated with significantly lower all grade adverse events (27.2% vs. 46.2%, $p < 0.001$) as well as lower grade 3–4 adverse events (5.1% vs. 7.6%, $p = 0.006$).

The activity of denosumab in maintaining bone health and its efficacy in patients with metastatic disease have led to the investigation of denosumab in early breast cancer. In the ABCSG-18 study, postmenopausal women who were treated with aromatase inhibitors were randomized to denosumab (60 mg every 6 months for 3 years) or placebo. Denosumab was associated with a significant improvement in bone health, reducing fractures by 50%. Of interest, there was also an improvement in DFS (HR = 0.82, 95% CI 0.69–0.98, $p = 0.03$) [52, 53]. However, the larger D-CARE study, which unlike ABCSG-18 was designed primarily to explore the effect of denosumab on breast cancer outcomes rather than bone health, did not show any effect of denosumab compared with placebo. In this trial, 4500 women received an intensive dosing of denosumab (120 mg every 3–4 weeks for 6 doses followed by every 3 months) or placebo for 5 years [54]. In contrast to the ABCSG-18 study, denosumab failed to show improvement in bone metastasis–free survival, DFS, or OS. This study included premenopausal women; however, subgroup analysis based on menopausal status did not affect results. A high risk of ONJ was notable with more than 5% of patients treated with denosumab suffering from this adverse event. Considering these results, bisphosphonates should remain the standard bone-targeted therapy for early-stage disease.

Treatment of cancer therapy–induced bone loss

The expected benefit of bisphosphonates in improving bone mineral density is of value in women with breast cancer. Osteopenia and osteoporosis are common comorbidities at the time of diagnosis, especially in postmenopausal women. Additionally, adjuvant treatment with chemotherapy and/or aromatase inhibitors may result in further decline of bone mineral density and increase the risk for bone fractures [55–59]. Upfront treatment with zoledronic acid in postmenopausal women treated with aromatase inhibitors was associated with better maintenance of bone mineral density compared with starting treatment only with evidence of decline in bone mineral density [58–60]. The results of the EBCTCG meta-analysis further support the importance of bisphosphonates in bone health with evidence of reduction in bone fractures with bisphosphonates compared with no treatment or placebo (RR 0.85, 95% CI 0.75–0.97; $p = 0.02$) [61]. Compared with bisphosphonates, denosumab has shown superiority in maintaining bone health in patients with osteoporosis [62]. As mentioned above, the ABCSG-18 study assessed the efficacy of denosumab on bone health in postmenopausal women who are treated

with aromatase inhibitors [52]. Denosumab was shown to significantly delay the first clinical fracture as well as to improve bone health compared with placebo [52].

Safety and Tolerability

Bisphosphonates are tolerated well, usually without serious side effects. Zoledronic acid and pamidronate often cause acute phase reaction commonly occurring within the 3 days after infusion, especially during the first few infusions [63]. Pyrexia, which occurs in about one-third of the patients, is the most common symptom, but myalgia, arthralgia, arthritis, swollen joints, and headache may also occur [63]. Hypocalcemia is a known complication of all bisphosphonates. Although hypocalcemia is uncommon and usually mild and asymptomatic, life-threatening hypocalcemia resulting in neurological symptoms and QTc prolongation has been reported [63]. Calcium levels, corrected for albumin, should be monitored in patients who are treated with bisphosphonates, and daily supplements of calcium and vitamin D are recommended during therapy. Renal toxicity is uncommon and is associated more commonly with intravenous bisphosphonates. Assessment of renal function before each infusion is required, and treatment can be given with dose adjustment as long as creatinine clearance is more than 30 mL/min [63]. Gastrointestinal symptoms, usually mild in severity, can occur and include nausea, vomiting, abdominal pain, and diarrhea. These side effects are more common with oral treatment [63]. Rarely, atypical bone fractures (subtrochanteric and diaphyseal femoral fractures) have been reported in patients receiving prolonged bisphosphonate treatment. These fractures occur often with minimal or no trauma and are slow to heal. If atypical fractures occur, bisphosphonate treatment should be discontinued [63]. ONJ is a serious complication of bisphosphonate treatment. The risk for ONJ is higher with intravenous than with oral bisphosphonate treatment and is more commonly observed with higher dose density and prolonged duration of treatment as used in patients with metastatic disease [63]. While ONJ is very rare or unreported with oral bisphosphonates, intensive scheduling of intravenous treatment is associated with an incidence of ONJ of up to 2% [64]. As preexisting dental disease and invasive dental procedures increase the risk for ONJ, dental assessment before initiation of bisphosphonate treatment as well as holding treatment during any planned dental procedures is recommended.

Conclusions

Bisphosphonates have an important role in the treatment of breast cancer and have been incorporated into standard treatment algorithms. For patients with metastatic disease to bone, treatment with bisphosphonates reduces the risk of SREs, which may improve quality of life, but these drugs do not have an effect on other breast cancer outcomes. Adjuvant treatment with zoledronic acid or oral clodronate should be considered for all postmenopausal women with early-stage cancer, although in very low-risk populations, omission of this

treatment is a reasonable option. Denosumab could be an alternative to bisphosphonates in the metastatic setting; however, current data do not support its routine use for early-stage disease.

Compliance with Ethical Standards

Conflict of Interest

Hadar Goldvaser declares that she has no conflict of interest.

Eitan Amir has received compensation from Genentech/Roche for the provision of expert testimony and from Apobiologix Agendia and Myriad Genetics for service as a consultant.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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