CLINICAL INVESTIGATION

Bisphosphonates in the adjuvant treatment of breast cancer: rationale and clinical data

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Bisphosphonates are established therapies for bone loss and for the prevention of skeletal-related events from bone metastases. Clinical trials in the early breast cancer setting suggested a potential anticancer role for clodronate a decade ago. Recent data from the Austrian Breast and Colorectal Cancer Study Group Trial 12 and one of the Zometa-Femara Adjuvant Synergy Trials (ZO-FAST) demonstrate that zoledronic acid can significantly improve disease-free survival when administered in the adjuvant setting concomitantly with endocrine therapy for breast cancer in the premenopausal and postmenopausal settings. Moreover, a recent subset analysis of the ongoing AZURE trial in patients with early breast cancer revealed that zoledronic acid can significantly reduce residual invasive tumor size, and improve pathologic complete response, versus neoadjuvant chemotherapy alone. There is a wealth of preclinical data illustrating multiple anticancer mechanisms of action of zoledronic acid that might underlie these clinical effects.

Keywords: adjuvant therapy • anticancer • bisphosphonate • breast cancer • zoledronic acid

Among women, breast cancer is the leading cause of cancer deaths and the most common cancer worldwide, with an estimated 1.3 million new cases each year [1]. Survival rates for patients with breast cancer are directly correlated with stage at diagnosis. For patients with localized disease (stage I and II), the 5-year survival rate is 98% versus 81% for patients with regional metastases (stage III), and only 26% for distant metastases (stage IV disease) [1,2].

Role of the bone microenvironment in facilitating breast cancer recurrence

The bone microenvironment provides a supportive niche for cancer cell survival and tumor growth [3,4]. Breast cancer cells have a natural predilection for metastasizing to the skeleton. Indeed, approximately 70% of patients with advanced breast cancer will develop bone metastases, and bone is the first site of metastasis in 30–40% of patients with relapsed disease [5]. The release of bone-derived growth factors and cytokines into the microenvironment can attract cancer cells to the bone surface and facilitate their growth and propagation [6]. In turn, many cancer cells secrete factors that can increase rates of bone resorption [6]. The dependence of metastasis on the link between cancer stem cells (the 'seeds') and the microenvironment (the 'soil') was first hypothesized by Stephen Paget more than a century ago, and this 'seed and soil' hypothesis has become especially meaningful to oncologists as our understanding of cancer–bone interactions has developed in recent years [7]. Indeed, the bone marrow is now also recognized as a sanctuary for harboring cancer 'seeds' for subsequent relapse in bone and other sites [3,4].

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Effects of cancer therapy on bone

In addition to the direct threat to bone from the cancer itself, treatment for breast cancer can also result in bone loss in many patients. The general consensus for treatment of early breast cancer includes surgical resection and systemic therapy (chemotherapy and targeted treatment as appropriate, together with long-term endocrine therapy for hormone receptor-positive breast cancer) [8]. Current diagnostic techniques and adjuvant therapies for breast cancer have led to an increase in disease-free survival (DFS). However, adjuvant treatments for breast cancer can negatively impact skeletal health: chemotherapy can cause ovarian failure and early menopause, leading to accelerated bone loss and osteoporosis [9]. Aromatase inhibitors (AIs) are now established as the treatment of choice for postmenopausal women with hormone-responsive breast cancer [8] and result in reduction of circulating estrogens to levels substantially lower than those observed after natural menopause [10]. In addition, ovarian suppression with a luteinizing hormone-releasing hormone (LHRH) agonist (e.g., goserelin) is extensively used in premenopausal patients with breast cancer and results in a rapid decrease in circulating estrogens to postmenopausal levels for the duration of treatment [8]. Low estrogen levels correlate with increased rates of osteolysis and resultant bone loss.

In the general population (i.e., in healthy women), hormone-replacement therapy (HRT) has been successful in preventing bone loss after natural or surgical menopause, although its use has been limited in recent years because of emerging safety concerns. In particular, the reported increase in breast cancer incidence in HRT users in large trials (e.g., the Million Women Study) [11] had a profound impact on HRT use. In general, HRT is contraindicated during adjuvant endocrine treatment for breast cancer, and might be unsafe in women who have completed therapy for hormone-responsive breast cancer because of its potential growth-promoting effect on residual tumor cells, which may lie dormant in the bone marrow and other niches. However, mechanistic data suggest that safe use of HRT might be possible in women with hormone receptor-negative breast cancers, although further clinical data are needed to confirm this [12].

Bisphosphonates

Bisphosphonates (BPs) are antiresorptive agents that inhibit osteoclast-mediated bone resorption [6,13]. By doing so, it is hypothesized that BPs may hinder the development of bone metastases and might render the bone microenvironment less conducive to cancer cell survival and proliferation. Moreover, some BPs have demonstrated additional mechanisms of action that may directly or indirectly interfere with cancer progression and tumor growth. Nitrogen-containing BPs, such as zoledronic acid (ZOL), inhibit the activity of farnesyl diphosphate synthase, a key enzyme in the mevalonate pathway of protein prenylation [13,14]. As a result, these agents interfere with the post-translational modification of key regulatory proteins and signaling intermediates (e.g., Rho and Rac), thereby influencing cellular activity, proliferation and viability [13,15].

In preclinical studies, BPs have been reported to have a direct effect on the survival, proliferation, invasiveness and adhesion of cancer cells (Figure 1) [15], especially in combination with chemotherapy [15,16]. Indeed, current preclinical data support anticancer synergy for BPs combined with cytotoxic agents as well as AIs [15,17–21], although some of these studies were performed using BP levels beyond those used in clinical practice. However, the clinical promise of the anticancer activity of BPs first described in preclinical studies is supported by translational data suggesting their ability to inhibit angiogenesis [22], modulate anticancer immune response [23]

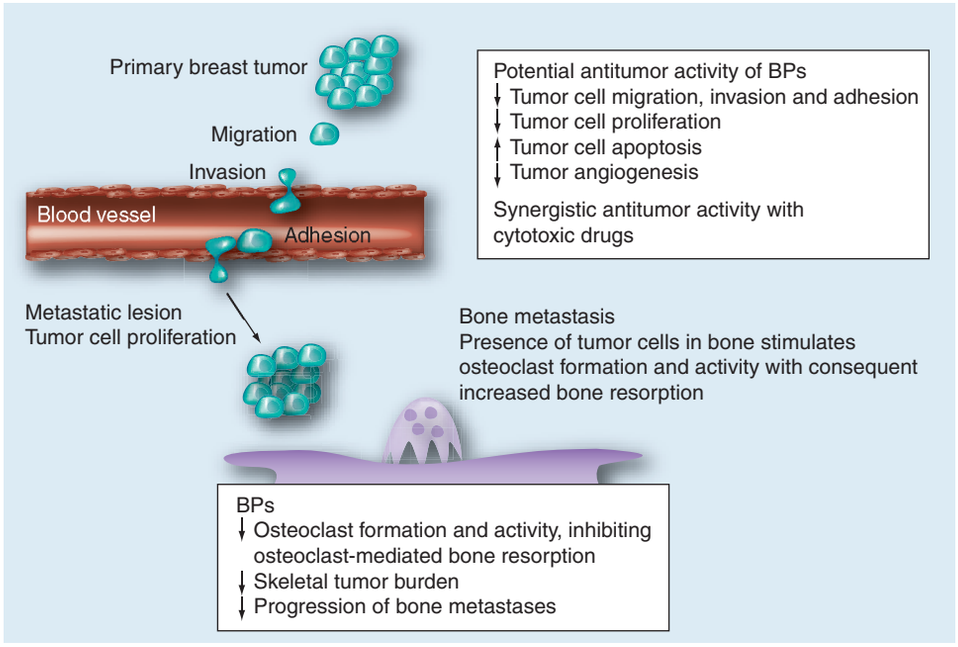

Figure 1. Multiple mechanisms of anticancer activity of bisphosphonates.
BP: Bisphosphonate.
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and inhibit the survival and persistence of breast cancer cells in bone marrow [24–27]. Moreover, recent clinical data indicate an emerging clinical activity of ZOL for increasing DFS and reducing distant recurrences in the early breast cancer setting [28–30], and it is likely that a variety of the anticancer mechanisms of action demonstrated in preclinical and translational studies may contribute to the observed clinical benefits. This review will summarize and critically examine the existing data supporting the potential anticancer activity of BPs in light of outcomes from recent clinical trials.

Bone-targeted agents for preventing disease recurrence

The seed and soil hypothesis provides a useful theoretical framework for evaluating breast cancer recurrence in women with early stage disease. The distribution of metastases does not appear to be random; rather, the soil of the bone microenvironment actually may promote cancer cell survival and tumor growth. Cancer cells often can be detected as disseminated tumor cells (DTCs) in the bone marrow or as circulating tumor cells (CTCs) in the blood of patients with breast cancer. Both DTCs and CTCs have been correlated with increased risks of disease recurrence and poor clinical outcomes [31,32]. The DTCs in particular may seed future cancer recurrence in and outside bone [33], and the specialized cellular interactions and signaling pathways in the bone marrow niche may inadvertently protect dormant DTCs from the cytotoxic and proapoptotic effects of systemic anticancer therapies [3,4].

Bone remodeling is controlled by a variety of local and systemic factors, and is characterized by coupled and balanced osteolysis followed by osteogenesis. Tumor cells destroy the balance between osteoclast-mediated bone resorption and the formation of new bone by osteoblasts [6]. As with all BPs, ZOL preferentially targets bone and is a key component of care for women with bone metastases from breast cancer. ZOL (in conjunction with standard anticancer therapy) is indicated for preventing skeletal-related events in patients with bone metastases from a variety of solid tumors and osteolytic lesions from multiple myeloma [34]. Moreover, ZOL has been shown to not only prevent bone loss [29,35–37], but also to improve DFS and reduce DTC levels during adjuvant therapy for breast cancer [24,27–30,38,39]. Recent hypothesis-generating studies (involving a total of >400 patients) demonstrated the capacity of ZOL to reduce DTC prevalence and persistence in women with breast cancer [24,27,28,38,39]. In one study, 120 women with newly diagnosed breast cancer were randomized to neoadjuvant chemotherapy with or without ZOL (4 mg every 3 weeks) for 1 year. Of the women who were DTC-positive at baseline, 70% of ZOL-treated patients were DTC-negative at 3 months, versus 53% in the chemotherapy-alone group ($p = 0.054$) [24]. In addition, 87% of ZOL-treated patients who were DTC-negative at baseline remained DTC-negative at 3 months, versus 60% of patients receiving chemotherapy alone ($p = 0.03$) [24]. A second study in 45 patients who were DTC-positive after completing adjuvant chemotherapy recently reported outcomes after 49 months' median follow-up [39]. In this study, treatment with monthly ZOL for 2 years significantly reduced the prevalence of DTCs at 12 and 24 months versus baseline ($p \leq 0.001$) [39]. Moreover, the favorable DFS at 49 months in this small study in patients with high-risk breast cancer is consistent with a potential long-term anticancer 'carry-over' benefit 2 years after ZOL treatment is completed (as discussed later in the section on ABCSG-12) [39]. ZOL was well tolerated in each of these studies [24,27,38,39].

The early and sustained reduction in DTC levels with ZOL treatment in these studies is of great interest because of a large body of evidence indicating that baseline and on-treatment DTC status correlates with reduced breast cancer-specific survival and shorter time to disease recurrence [31,40–42]. Therefore, it is likely that the early reduction in DTCs with ZOL treatment may translate into prolonged DFS and overall survival (OS) for these patients.

Preclinical rationale & translational studies support the anticancer activity of BPs

The last decade witnessed the accumulation of a large body of preclinical evidence supporting the ability of BPs to inhibit tumor growth and metastasis in a variety of malignancies [15,18–21,43–46]. In addition to direct inhibition of cancer cell proliferation, clinically relevant doses of ZOL were shown to inhibit tumor growth in animal models of breast cancer [44]. Anticancer mechanisms of action observed in preclinical studies of BPs include direct inhibition of cell proliferation and viability, induction of apoptosis, impaired angiogenesis, interference with cancer cell invasion and adhesion, and synergy with anticancer therapies [15–21,44–51]. Inhibition of the mevalonate pathway by nitrogen-containing BPs interferes with the post-translational modification (farnesylation and geranyl-geranylation) and activity of key signaling proteins, such as Ras and Rho [52]. These effects are believed to contribute to the anticancer activities of BPs *in vitro* and *in vivo*. The mevalonate pathway has been extensively studied for the design of new anticancer agents, and preclinical studies show promising anticancer potential for several different approaches to inhibiting this pathway [53,54]. However, unlike BPs, some agents (e.g., farnesyltransferase inhibitors) have fallen short in clinical studies [55]. Thus, it is possible that the promising anticancer activity of BPs results

from a combination of bone targeting, long *in vivo* half-life in the bone microenvironment and structural aspects of BPs that contribute to effective inhibition of the mevalonate pathway.

Translational studies demonstrate that ZOL can also reduce the levels of angiogenic growth factors and induce activation of γδ T cells (components of the anticancer immune response) in patients with breast cancer and other malignancies [22,23,56–60]. Given the complexity and multiplicity of mechanisms involved in metastasis of solid tumors, it is likely that several of these anticancer effects of BPs on the process of metastasis combine to produce the clinical benefits observed in recent clinical trials.

Clinical studies

The potential anticancer activities of BPs have been investigated in prospective, large-scale, randomized, controlled studies in patients with breast cancer.

Adjuvant clodronate trials

The effectiveness of clodronate (CLO) alone or combined with chemotherapy and/or hormonal therapy in preventing breast cancer metastasis to bone was evaluated in three clinical trials that yielded promising but inconsistent results [61–63]. For example, in a randomized trial in 302 patients with bone marrow micrometastases from breast cancer, treatment with oral CLO (1600 mg/day for 2 years) significantly reduced the incidence of skeletal and visceral metastases versus the control group at 36 months median follow-up (p = 0.003) [61]. The 8.5-year follow-up of this trial demonstrated significant improvement in OS (p = 0.049) in the CLO group compared with the control group (suggesting carry-over survival benefits from 2 years of CLO treatment), although reductions in skeletal and visceral metastases did not retain statistical significance past the 55-month follow-up (Table 1) [61,64,65]. By contrast, in a similarly designed trial in 299 patients with node-positive breast cancer receiving the same dosage of CLO or control for 3 years, there was no reduction in the development of skeletal metastases after 5 years of follow-up [63]. Rates of bone metastasis remained similar between treatment groups after 10 years of follow-up [66]. Indeed, in this trial CLO appeared to correlate with reduced DFS, potentially because of elevated rates of visceral metastases [63,66]. Although interpretation of data from this trial is complicated by imbalances in baseline prognostic factors between treatment arms as well as numerous secondary randomizations [5], it remains evident that treatment with CLO did not significantly alter the rate of bone metastasis in this patient population.

In a larger-scale randomized, double-blind, placebo-controlled trial of CLO, 1069 patients with primary operable stage I–III breast cancer were randomized to oral CLO (1600 mg/day) or placebo for 2 years in conjunction with standard treatment (surgery, radiotherapy, adjuvant chemotherapy and/or tamoxifen) for primary breast cancer, and were assessed for bone metastases over a 5-year study period [62]. A significant reduction of bone metastases (hazard ratio [HR]: 0.692; p = 0.043) and improved OS (HR: 0.768; p = 0.048) were reported for the CLO group versus placebo [62]. Overall, meta-analysis of the adjuvant CLO trials failed to show any

Table 1. Incidence of metastatic disease and death in patients receiving clodronate versus placebo.

Follow-up (months)†	Outcome	Patients, n (%)		p-value	Ref.
		Clodronate (n = 157)	Placebo (n = 145)		
36	Distant metastases	21 (13.4)	42 (29.0)	<0.001	[61]
	Bone metastases	12 (7.6)	25 (17.2)	0.003	
	Visceral metastases	13 (8.3)	27 (18.6)	0.003	
	Deaths	6 (3.8)	22 (15.2)	0.001	
55	Distant metastases	32 (20.4)	51 (35.2)	0.022	[64]
	Bone metastases	20 (12.7)	34 (23.4)	0.044	
	Visceral metastases	24 (15.3)	37 (25.5)	0.091	
	Deaths	13 (8.3)	32 (22.1)	0.002	
103	Distant metastases	61 (38.9)	57 (39.3)	0.816	
	Bone metastases	37 (23.6)	38 (26.2)	0.770	
	Visceral metastases	33 (21.0)	32 (22.1)	0.222	
	Deaths	32 (20.4)	59 (40.7)	0.049	

†All follow-up durations are medians.
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significant advantage in terms of bone metastases prevention (HR: 0.68; 95% CI: 0.38–1.23) or improvement in OS (HR: 0.75; 95% CI: 0.31–1.82) [67]. Nonetheless, these early trials with CLO laid the groundwork for later trials with more active BPs such as ZOL, and recent evidence from the multiple myeloma setting supports better anticancer activity with ZOL (a nitrogen-containing BP) compared with CLO (a non-nitrogen-containing BP) in terms of prolonged OS [68,69].

Adjuvant ZOL trials

■ Z-/ZO-/E-ZO-FAST trials

In postmenopausal women with breast cancer, adjuvant AI therapy is associated with accelerated bone loss and increased risk of fractures [70,71]. The activity of ZOL for preventing such bone loss was evaluated in the three companion Zometa-Femara Adjuvant Synergy Trials: Z-FAST (n = 602), ZO-FAST (n = 1065) and E-ZO-FAST (n = 527), in postmenopausal women receiving adjuvant letrozole therapy for stage I–III breast cancer [72,73]. Patients with baseline lumbar spine (LS) and total hip (TH) T-scores of -2.0 or greater were randomized to upfront or delayed-start intravenous ZOL (4 mg every 6 months for 5 years). Delayed-start ZOL was initiated for substantial decreases in bone health (i.e., postbaseline T-score < -2.0, or low-trauma fracture) [29,72]. The primary end point in each trial was change in LS bone mineral density (BMD) between baseline and 12 months [72]. Secondary end points included changes in TH BMD, disease recurrence and safety. The difference in LS BMD between the upfront- and delayed-ZOL arms was approximately 9% (increase of 4% to 6% in the upfront-ZOL groups vs decrease of 3% to 4.9% in the delayed-ZOL groups; p < 0.0001 for each trial) after a median follow-up of 36 months in ZO-FAST and E-ZO-FAST; after 61 months' follow-up in Z-FAST, LS BMD increased by 6.19% on average with upfront ZOL versus a decrease of 2.42% with delayed ZOL [29,74,75]. Interestingly, the difference in BMD was maintained, and even increased progressively, despite increasing numbers of patients initiating ZOL in the delayed arm (approximately 25% of delayed-ZOL patients in the Z-FAST study had initiated ZOL by the 48-month time point) [74]. Although none of these trials were designed or powered to detect significant differences in fracture incidence, the number of fractures was consistently lower in the upfront-ZOL groups versus the delayed-ZOL groups in each study (28 vs 33 in Z-FAST, 26 vs 32 in ZO-FAST and 5 vs 12 in E-ZO-FAST, respectively) [29,74,75].

Disease recurrence and DFS were assessed as secondary end points in these trials. In the largest of the three trials (ZO-FAST, n = 1065), addition of upfront ZOL to AI therapy was associated with a 41% reduction in the risk of DFS events (disease recurrence or death) compared with delayed ZOL (p = 0.0314; Figure 2) [29,30] after a median follow-up of 36 months [29]. Interestingly, patients receiving upfront ZOL had fewer breast cancer recurrences at skeletal and extraskeletal sites (Figure 3) [5,29]. The observed DFS benefit with upfront ZOL consistently increased between 12 and 48 months follow-up in this trial (HR: 0.59; p = 0.0175) [29,72,76], despite approximately 25% of patients initiating ZOL in the delayed group [77]. In the two smaller trials, Z-FAST (n = 602) and E-ZO-FAST (n = 527), there were no significant differences in proportions of patients with DFS events for upfront versus delayed ZOL (p = 0.6283 after 61 months follow-up in Z-FAST and p = 0.1397 after 36 months follow-up in E-ZO-FAST) [77]. These results suggest that the event rates in Z-FAST and E-ZO-FAST are too low to detect statistically significant DFS differences between treatment groups in this relatively low-risk patient population, especially given the trial design (i.e., rescue therapy, which has resulted in up to a quarter of patients in the delayed arm initiating ZOL) [77]. Indeed, integrated analysis of Z-FAST and ZO-FAST (total n = 1667) revealed significantly reduced disease recurrence at as early as 12 months median follow-up (p = 0.0401) [72], and a 43% reduced risk of DFS events by Kaplan–Meier analysis at 24 months follow-up (p = 0.0183) [76]. Further analyses, including DFS assessments censoring patients who initiated ZOL in the delayed arms, may provide further insight into the effects of ZOL on disease recurrence in these trials.

■ Austrian Breast & Colorectal Cancer Study Group Trial 12

The Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12; n = 1803) was a 3-year, randomized, Phase III trial comparing the efficacy

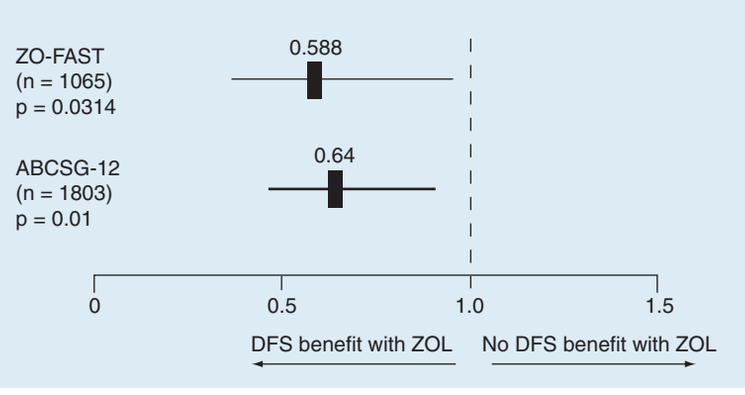

Figure 2. Adding zoledronic acid to adjuvant endocrine therapy improves disease-free survival in postmenopausal (ZO-FAST) and premenopausal (ABCSG-12) women with early breast cancer.

CI: Confidence interval; DFS: Disease-free survival; ZOL: Zoledronic acid (4 mg every 6 months).

Data from [29,30].

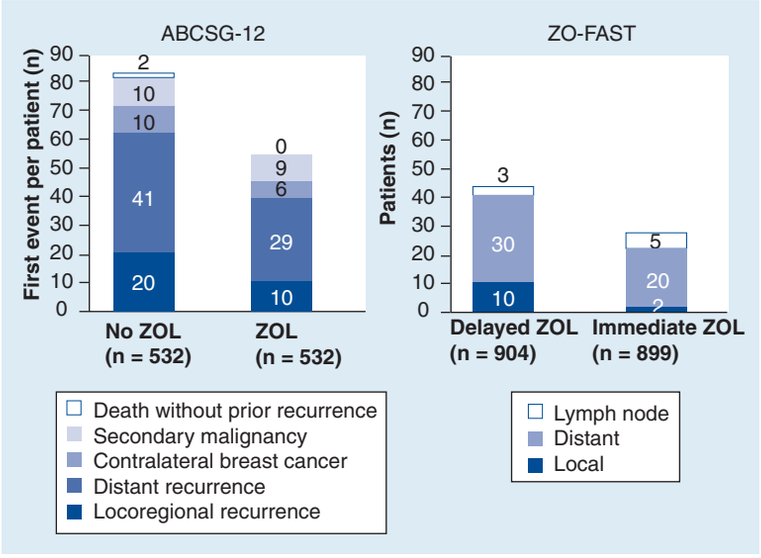

Figure 3. Adding zoledronic acid (4 mg every 6 months) to adjuvant endocrine therapy reduces breast cancer recurrences in and outside bone in postmenopausal (ZO-FAST) and premenopausal (ABCSG-12) women. Multiple sites of metastases may be reported for the same patient. Sites of distant metastases include bone, brain, liver, lung, skin, lymph node and other.
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of tamoxifen (20 mg/day orally) versus anastrozole (1 mg/day orally), with or without ZOL (4 mg every 6 months) in premenopausal women with early-stage, hormone-responsive breast cancer undergoing ovarian suppression with goserelin (3.6 mg subcutaneously every 28 days) [30]. The primary end point of the study was DFS (tamoxifen vs anastrozole, and ZOL vs no ZOL). Secondary end points included recurrence-free survival (RFS), OS, safety, and BMD assessments in a protocol-defined substudy [30,35]; bone metastasis-free survival was assessed as an exploratory end point.

The primary efficacy analysis after 48 months median follow-up showed that adding ZOL to adjuvant endocrine therapy reduced the risk of DFS events by 36% (HR: 0.64; log-rank p = 0.01; Figure 2) [29,30] compared with endocrine therapy alone [30]. Patients receiving ZOL also had a 35% reduced risk of RFS events compared with patients receiving no ZOL (p = 0.02), and showed a trend toward improved OS (HR: 0.60; p = 0.11) [30]. The addition of ZOL to endocrine therapy was associated with reduced disease recurrences at all sites of measurement (54 first DFS events with ZOL vs 83 in the no-ZOL group [Δ = 29]; Figure 3) [5]. After 62 months follow-up of the ABCSG-12 trial, 2 years after treatment completion, the addition of ZOL to endocrine therapy continued to produce durable improvements in DFS (76 DFS events with ZOL vs 110 in the no-ZOL group [Δ = 34]; HR: 0.68; log-rank p = 0.008) and a continued trend toward improved OS (HR: 0.665; log-rank p = 0.094) compared with endocrine therapy alone [78]. These long-lasting benefits from adding ZOL to adjuvant endocrine therapy are consistent with the benefits from CLO in the study by Diel *et al.* [65], and argue in favor of a potential carryover benefit from BP therapy for early breast cancer even after long-term BP treatment is completed. There were no differences in DFS outcomes between tamoxifen- and anastrozole-treated patients at the 48- or 62-month time points [30,78]. This is in contrast to the postmenopausal setting, in which AIs (letrozole as well as anastrozole) have been shown to improve DFS beyond that achieved with tamoxifen [79,80].

Results from the bone substudy of ABCSG-12 (n = 404) showed that patients receiving endocrine therapy plus ZOL had stable LS BMD after 36 months, compared with a significant decrease of 11.3% versus baseline in patients receiving endocrine therapy alone (p < 0.0001) [35]. Analyses after a median follow-up of 60 months (2 years after completion of therapy) showed that BMD had recovered somewhat in the endocrine therapy group, but remained significantly below baseline (-6.3% at LS; p = 0.001) [35]. On the other hand, BMD increased above baseline in patients who had received ZOL in addition to endocrine therapy (+4.0% at LS; p = 0.02) [35].

AZURE trial

An ongoing prospective trial in patients with stage II/III breast cancer (Does Adjuvant ZOL Reduce Recurrence in Patients with High-risk Localised Breast Cancer? [AZURE]; n = 3360) is currently evaluating a tapered dosing schedule of ZOL (monthly for 6 months, then quarterly for 2 years, then twice yearly, for a total treatment duration of 5 years) [28]. Unlike the Z-/ZO-/E-ZO-FAST and ABCSG-12 trials, this study is not limited to hormone-responsive breast cancer, and will evaluate ZOL combined with adjuvant chemotherapy as well as endocrine therapy. In a prespecified subset analysis of patients who received neoadjuvant chemotherapy (n = 205), adding ZOL reduced mean residual invasive tumor size by approximately 44% compared with chemotherapy alone (15.5 vs 27.4 mm; p = 0.006) [28]. In addition, patients receiving neoadjuvant chemotherapy with ZOL had an approximately twofold higher rate of pathologic complete response versus neoadjuvant chemotherapy alone (11.7 vs 6.9%) [28]. Complete efficacy and safety analyses from this event-driven trial are awaited.

BP safety in the adjuvant setting

Data from ABCSG-12, Z-/ZO-/E-ZO-FAST, and the AZURE neoadjuvant subset, as well as from the Phase II DTC suppression trials, show that the

combination of ZOL with (neo)adjuvant therapy is generally well tolerated, with very few instances of renal adverse events or osteonecrosis of the jaw (ONJ) [24,27,28,30,38,39,77]. There were no cases of serious renal adverse events or ONJ in the ABCSG-12 trial [30]. In Z-/ZO-/E-ZO-FAST after follow-up periods of 36 to 61 months, the frequency of grade 3 or 4 renal adverse events ranged between 0.27% in patients receiving delayed ZOL and 0.37% in patients receiving upfront ZOL; the overall incidence of ONJ was 0.2% in these trials [77]. Although trials of CLO and pamidronate in the adjuvant setting did not report detailed adverse event data [62,65,66,81], primary publications from these trials suggest that treatment is well tolerated overall [62,65,66]. The SWOG 0307 study is an ongoing large, head-to-head, Phase III trial (n = 6097) comparing 3 years of treatment with ZOL, CLO or ibandronate (another oral BP) in the early breast cancer setting, and is expected to provide insight into the relative tolerability and convenience of these agents.

Future perspective

The role of BPs in early breast cancer is rapidly evolving. Several BPs and the novel bone-targeted agent denosumab have demonstrated activity to prevent bone loss associated with adjuvant therapy for breast cancer (reviewed in Lipton [82]). More importantly, evidence for the anticancer activity of BPs is rapidly accumulating. Adding ZOL to adjuvant endocrine therapy clearly improves DFS in premenopausal and postmenopausal women with early breast cancer [29,30], and clinical data supporting the combination of ZOL with chemotherapy are emerging [28]. Recent data from large population-based studies suggest that long-term treatment with oral BPs for osteoporosis may reduce the risk of invasive breast cancer in postmenopausal women [83–85]. An ongoing clinical trial program is evaluating the anticancer potential of bone-targeted agents in the adjuvant therapy setting in several thousand women with early-stage breast cancer (e.g., ibandronate in GAIN [n = 3024], CLO in NSABP B34 [n = 3400], ZOL vs ibandronate vs CLO in SWOG 0307 [n = 6097], ZOL in SUCCESS [n = 3754] and NATAN [n = 693], and denosumab in ABCSG-18 [n = 3400] and D-CARE [n = 4500]). In addition, BPs have demonstrated promising anticancer activity in other malignancies in which the skeleton plays a key role. Clodronate improved OS in men with bone metastases from hormone-sensitive prostate cancer in one trial [86]; however, BPs have yet to demonstrate a significant survival benefit in prostate cancer patients with localized disease or patients with bone metastases from castration-resistant (hormone-refractory) prostate cancer [86–90]. Nonetheless, there have been some reports of OS benefits with ZOL treatment in some other advanced cancer settings [91,92]. Recently, in the first head-to-head comparison between two BPs, ZOL was shown to improve OS versus CLO in patients with multiple myeloma (n = 1960) [68]. The anticancer potential of ZOL is being evaluated in ongoing trials in prostate cancer and other settings [5], and results from these clinical trials are expected to help elucidate the potential of BPs to alter the disease course in these malignancies.

Bisphosphonates appear to be poised for expanded use in the breast cancer setting over the next few years. Routine use of BPs to prevent bone loss during adjuvant therapy is likely to become the norm, especially for patients receiving endocrine therapy. The potential use of oral BPs for preventing invasive breast cancer is exciting and provocative, but requires prospective evidence before becoming routine practice in primary prevention of breast malignancies. Because a prevention strategy would expose a large proportion of healthy women to pharmacologic intervention, a better understanding of the risk-benefit ratio and strategies to identify women most likely to benefit from such preventive intervention are needed before preventive BP therapy can be recommended. Nonetheless, the growing body of evidence supporting the anticancer effects of ZOL is likely to increase its use as adjuvant therapy combined with endocrine agents, and with chemotherapy in the neoadjuvant setting. The AZURE trial is evaluating the use of ZOL in patients receiving adjuvant chemotherapy and/or endocrine therapy, and a large ongoing clinical trial program is investigating BPs and other bone-targeted agents as components of adjuvant therapy in breast cancer. As data from these studies mature, it is likely that BPs will become a routine part of the clinical management of breast cancer.

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Executive summary

Background

- Among women worldwide, breast cancer is the most common malignancy and a leading cause of death.
- The predilection of breast cancer to metastasize to bone provides a strong rationale for using bone-directed agents, such as bisphosphonates, to prevent disease recurrence.
- The bone microenvironment is highly conducive to the survival and proliferation of cancer cells, especially dormant disseminated tumor cells (DTCs).
- The specialized cell–cell contacts and signaling pathways in the bone marrow niche unwittingly may protect DTCs from the cytotoxic and proapoptotic effects of systemic anticancer treatment.

Preclinical evidence for the anticancer activity of bisphosphonates

- Bisphosphonates have been shown to block multiple steps in tumor metastasis.
- Bisphosphonates can directly affect cancer cell proliferation and viability, as well as synergize with anticancer therapies.
- Bisphosphonates can also block key processes in metastasis (e.g., angiogenesis, invasion and adhesion).

Translational evidence for the anticancer activity of bisphosphonates

- Adding zoledronic acid to standard treatment has been shown to reduce the persistence of DTCs in patients with early-stage breast cancer and DTC-positive bone marrow after adjuvant chemotherapy.
- In pilot trials, intravenous bisphosphonates have reduced circulating levels of proangiogenic factors (e.g., VEGF) in patients with breast cancer.
- Zoledronic acid has been shown to activate anticancer immune responses via activating γδ T cells.

Clinical evidence for the anticancer benefits of bisphosphonates

- Early clinical trials with adjuvant clodronate provide promising but inconsistent evidence for prevention of bone metastases by bisphosphonates.
- Recent Phase III trials clearly demonstrate that adding zoledronic acid (ZOL) to adjuvant endocrine therapy for breast cancer improves disease-free survival, together with reduced disease recurrences in and outside bone.
- Adding ZOL to neoadjuvant chemotherapy for early breast cancer reduces residual tumor size and improves pathologic response rates.
- Ongoing trials are evaluating the potential anticancer activity of ZOL and other bone-directed agents in breast cancer.
- Outstanding questions include the effect of bisphosphonates on overall survival, their efficacy in combination with cytotoxic agents and targeted therapies (e.g., trastuzumab), and the real-world likelihood of patients complying with therapy.
- Finally, recent data suggest a potential role for bisphosphonates in breast cancer prevention. Although it is too early to recommend such use of bisphosphonates, future research in this setting will help elucidate the possible preventive benefits of these agents. In addition, these recent data may prove a useful motivator for osteoporotic and osteopenic women to persist with bisphosphonate treatment.

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