

Bones, breasts, and bisphosphonates: rationale for the use of zoledronic acid in advanced and early breast cancer

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Abstract: Bisphosphonates inhibit osteoclast-mediated bone resorption, thereby inhibiting the release of growth factors necessary to promote cancer cell growth, differentiation, and tumor formation in bone. These agents have demonstrated efficacy for delaying the onset and reducing the incidence of skeletal-related events in the advanced breast cancer setting, and have been shown to prevent cancer therapy-induced bone loss in the early breast cancer setting. Emerging clinical data indicate that the role of bisphosphonates in advanced and early breast cancer is evolving. Retrospective analyses and recent clinical trial data show that zoledronic acid may improve outcomes in some patients with breast cancer. Data from ABCSG-12 and ZO-FAST suggest that zoledronic acid may improve disease-free survival in the adjuvant breast cancer setting in postmenopausal women or women with endocrine therapy-induced menopause, and recent data from a predefined subset of the AZURE trial added to the anticancer story. However, the overall negative AZURE trial also raises questions about the role of bisphosphonates as an anticancer agent in patients with breast cancer. Overall, these data suggest that the addition of zoledronic acid to established anticancer regimens may have potential anticancer benefits in specific patient populations, although more studies are required to define its role.

Keywords: anticancer, adjuvant therapy, bone metastasis, skeletal, zoledronic acid

The burden of bone metastases in women with advanced breast cancer

The impact of breast cancer continues to be felt worldwide with more than 1 million new cases identified each year,¹ and 254,650 new cases in 2009 in the United States alone.² Although the primary tumor is often effectively treated with surgical resection and chemotherapy or endocrine therapy, cancer cells that escape the local site have a predilection for metastasis to bone, an environment that may help them survive during adjuvant therapy. As a result, distant metastases can develop in bone. Approximately 65% to 75% of women with advanced breast cancer will ultimately develop bone metastases, which can lead to skeletal-related events (SREs) such as pathologic fractures, spinal cord compression, hypercalcemia of malignancy, bone pain requiring palliative radiotherapy, and orthopedic surgery.³ Skeletal-related events can be severely debilitating, and may result in a significant reduction in functional independence and quality of life. Furthermore, SREs are associated with increased morbidity and mortality, and pathologic fractures have been associated with a significant increase in the risk of death in women with advanced breast cancer (32%; $P < 0.01$).⁴

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Managing bone metastases with bisphosphonates

Women with bone metastases from breast cancer often require palliative therapy (radiotherapy and analgesics) to prevent further bone destruction and to manage the pain associated with malignant bone disease. The presence of bone lesions frequently leads to an increase in the rate of osteoclast-mediated bone resorption. Bisphosphonates, antiresorptive agents that inhibit osteoclast function, have demonstrated efficacy for delaying the onset and reducing the incidence of SREs and controlling pain.^{5–8} During bone resorption, bisphosphonates bind to mineralized bone surfaces and are ingested by osteoclasts, wherein they block activation signals and can induce apoptosis.

Clodronate, ibandronate, pamidronate, and zoledronic acid (ZOL) are bisphosphonates that have demonstrated efficacy for delaying the onset and reducing the incidences of SREs and reducing the pain associated with bone metastases.⁹ These bisphosphonates have demonstrated varying activity in SRE-prevention trials in patients with multiple myeloma, metastatic breast cancer, prostate cancer, and lung cancer (Table 1).^{10–29} However, it should be noted that pamidronate and ZOL are the only bisphosphonates approved in the metastatic breast cancer setting in the United States.^{30,31} Recently, the antiresorptive agent denosumab also gained approval in the United States for the prevention of SREs in patients with bone metastases from solid tumors, including breast cancer.³² Current National Comprehensive Cancer

Network (NCCN) guidelines for breast cancer recommend initiation of antiresorptive therapy (ZOL, pamidronate, or denosumab) if there is plain radiographic evidence of bone destruction, and continuation of antiresorptive therapy until there is substantial decline in patient performance status.³³ Antiresorptive therapy is not currently recommended for the prevention of bone metastases.

However, evidence suggests that the benefits of bisphosphonates may extend beyond the reduction of SREs in patients with breast cancer. Preclinical trials have demonstrated that this class of agent has anticancer effects.³⁴ Anticancer activities include direct inhibition of cancer cell proliferation, induction of apoptosis, synergy with cytotoxic anticancer therapies, inhibition of angiogenesis, and activation of antitumor T-cell immunity. Moreover, modifying the bone microenvironment surrounding cancer cells may have powerful anticancer effects.^{35,36} Within the bone marrow, the release of bone matrix-derived growth factors by cancer cells during osteoclast-mediated bone resorption can promote cancer cell growth, differentiation, and tumor formation in bone. Inhibition of osteoclast-mediated bone resorption by bisphosphonates can prevent the release of these growth factors, thereby potentially preventing cancer recurrence.

Additional insights into the effects of the bisphosphonates ZOL and pamidronate on clinical outcomes have been reached through the retrospective analyses of biochemical markers of bone turnover. These markers may indicate the severity of metastatic bone disease. For example, elevated

Table 1 Summary of BP SRE prevention trials outcomes

Author	BP	Dosage	Tumor type	N	SRE risk reduction	P value
Lahtinen 1992 ¹⁹	CLO	2400 mg q day PO for 2 yr	MM	350	Yes	<0.001 ^a
McCloskey 1998 ²¹	CLO	1600 mg q day PO	MM	536	Yes	≤0.06
Brincker 1998 ¹⁴	PAM	300 mg q day PO	MM	300	No	0.27
Berenson 1998 ¹⁰	PAM	90 mg IV q 4 wk for 21 cycles	MM	392	Yes	0.015
Menssen 2002 ²²	IBN	2 mg IV q mo for 12–24 mo	MM	198	No	NS
Berenson 2001 ¹¹	ZOL; PAM	2 or 4 mg IV q mo; 90 mg	MM	280	Yes	<0.05 ^b
Rosen 2001, 2003 ^{24,25}	ZOL	4 or 8 mg IV q 3–4 wk	MM/BC	1648	Yes	0.025
Gimsing 2010 ¹⁶	PAM	30 or 90 mg IV q mo for 3 yr	MM	504	Yes	NS
Kohno 2005 ¹⁷	ZOL	4 mg IV q 4 wk for 1 yr	BC	228	41%	0.019
Aredia study 18 and 19 2000 ²⁰	PAM	90 mg IV q 3–4 wk	BC	751	23%	<0.001 ^c
Body 2003 ¹²	IBN	6 mg IV q 3–4 wk	BC	312	18%	0.04 ^c
Body 2004 ¹³	IBN	50 mg q day PO	BC	564	14%	0.08 ^c
Kristensen 1999 ¹⁸	CLO	1600 mg q day PO	BC	100	31%	0.03 ^c
Paterson 1993 ²³	CLO	1600 mg q day PO	BC	173	17%	0.03 ^c
Tubiana-Hulin 2001 ²⁹	CLO	1600 mg q day PO	BC	144	8%	0.03 ^c
Dearnaley 2003 ¹⁵	CLO	2080 mg q day PO	PC	311	Yes	0.02
Small 2003 ²⁸	PAM	90 mg IV q 3 wk	PC	378	No	NS
Saad 2002 ²⁷	ZOL	4 or 8 mg IV q 3–4 wk	PC	643	11%	0.02
Rosen 2003 ²⁶	ZOL	4 or 8 mg IV q 3–4 wk	LC	773	Yes	0.017

Notes: ^aSRE of pain only; ^bSRE of radiation to bone only; ^cPercentage decrease in SRE risk and P value derived from the Cochrane database meta-analysis.⁹

Abbreviations: BC, breast cancer; BP, bisphosphonate; CLO, clodronate; IBN, ibandronate; IV, intravenous; LC, lung cancer; MM, multiple myeloma; mo, month; NS, not significant; PAM, pamidronate; PC, prostate cancer; PO, orally; q, every; SRE, skeletal-related event; ZOL, zoledronic acid.

urinary N-telopeptide of type I collagen (NTX) levels are associated with increased risk of SREs, disease progression, and death.^{37,38} An exploratory analysis of patients with breast cancer, prostate cancer, myeloma, and non-small cell lung cancer found that approximately 30% of women with bone metastases from breast cancer have high NTX levels (≥ 100 nmol/mmol creatinine).³⁸ Patients with high and moderate NTX levels had a 2-fold increase in their risk of skeletal complications and disease progression compared with patients with low NTX levels ($P < 0.001$ for all). High NTX levels in each solid tumor category were associated with a 4- to 6-fold increased risk of death on study, and moderate NTX levels associated with a 2- to 4-fold increased risk compared with low NTX levels ($P < 0.001$ for all).³⁸ In a retrospective subset analysis of a phase III trial comparing ZOL with pamidronate in patients with breast cancer,³⁹ 60% of patients had elevated baseline NTX levels. Most patients (76%) treated with ZOL normalized their NTX levels after 3 months of therapy, and normalization of NTX significantly reduced the risk of SREs and improved survival (Figure 1).³⁹

Similar effects of ZOL were observed in a retrospective analysis of 3 large, phase III trials (N = 1341) in patients with breast cancer (n = 578), prostate cancer (n = 472), or non-small cell lung cancer and other solid tumors (n = 291) and elevated baseline NTX levels, which found that ZOL normalized or maintained normal NTX levels in most patients with bone metastases.⁴⁰ Indeed, normalization of NTX levels within 3 months of treatment was associated with reduced risks of skeletal complications and death compared with persistently elevated NTX.⁴⁰

In addition to studies in breast cancer, ZOL has also demonstrated survival benefits in several prospective studies in other tumor types. Notably, ZOL has shown improved survival in small pilot studies with patients with metastatic bladder cancer⁴¹ or multiple myeloma,⁴² and in a large phase III clinical trial in patients with multiple myeloma (N = 1960).⁴³ Together, these data support the potential

survival benefits of ZOL in patients with bone metastases from advanced cancer.

Adjuvant zoledronic acid therapy in early breast cancer

Current techniques for screening and early diagnosis of breast cancer and refinement of first-line and adjuvant treatments for breast cancer have led to increased survival in this setting. However, chemotherapy often causes ovarian failure and early menopause, which leads to osteoporosis.⁴⁴ The use of hormone replacement therapy is successful in preventing bone loss after natural and surgical menopause, but it cannot be utilized in breast cancer survivors because of its potential effect on dormant tumor cells.⁴⁵ Moreover, estrogen-depleting regimens are common adjuvant therapies for early breast cancer, and have been associated with significantly increased risk of fractures.^{6,46,47} The use of antiresorptive therapy is beneficial in this setting for preventing bone loss, and ZOL has consistently protected against bone loss associated with ovarian ablative and adjuvant hormonal therapies for early breast cancer. Furthermore, ZOL therapy may have effects beyond bone health in patients with early breast cancer.^{48,49}

In preclinical models, ZOL has been shown to block breast cancer metastasis to bone,⁵⁰ thereby preventing the vicious cycle of bone resorption and tumor formation. Data from translational clinical trials suggest that ZOL may affect the viability of cancer cells via its effects on bone metabolism.^{51–54} Indeed, ZOL may modify the bone microenvironment surrounding cancer cells through indirect effects on the ability of disseminated tumor cells (DTCs) to survive and/or reactivate to initiate tumor recurrence.³⁶ This concept has been supported by studies of the effects of ZOL on DTCs. The detection of DTCs in the bone marrow of women with early stage breast cancer is prognostic of early relapse.^{55,56} DTCs can lie dormant in bone marrow for extended periods of time before becoming active and metastasizing to secondary sites.³⁶

In pilot clinical trials in patients with breast cancer, ZOL reduced DTC persistency (Table 2).^{51,53,54,57} In one study, 120 patients with newly diagnosed breast cancer received 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 became DTC-negative by 3 months, versus 53% in the chemotherapy-alone group ($P = 0.054$).⁵¹ Furthermore, 87% of ZOL-treated patients who were DTC-negative at baseline remained DTC-negative at 3 months compared with 60% of patients receiving chemotherapy alone ($P = 0.03$).⁵¹ Patients who were DTC-positive after completing adjuvant

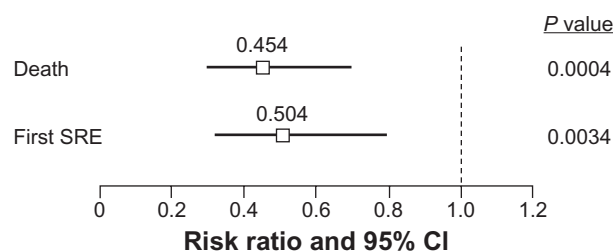


Figure 1 Kaplan–Meier estimates of survival by baseline and 3-month N-telopeptide of type I collagen (NTX) levels in women with bone metastases from BC.

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Abbreviations: CI, confidence interval; SRE, skeletal-related event.

Table 2 Effect of ZOL on DTC levels in patients with early breast cancer

Study	N	Adjuvant chemo/endocrine therapy ± ZOL dose	Results
Aft 2010 ⁵¹	120	4 mg q 3 wk IV × 1 yr	Among patients with DTC ⁺ BM at baseline, ZOL ↓ percentage of patients with persistent DTC at 3 mo ($P = 0.054$) vs no ZOL
Lin 2008 ⁵⁷	45	4 mg q mo IV × 2 yr	ZOL ↓ DTC number in BM at 12 mo ($P = 0.0006$, $n = 36$) and 24 mo ($P = 0.0026$, $n = 24$) vs baseline
Rack 2010 ⁵³	172	4 mg q mo IV × 6 mo	ZOL ↓ percentage of patients who remained DTC ⁺ at 6 mo ($P = 0.099$) vs no ZOL
Solomayer 2008 ⁵⁴	76	4 mg q mo IV × 24 mo	Among patients with DTC ⁺ BM at baseline, ZOL ↓ percentage of patients with persistent DTC at 12 mo ($P = 0.009$) vs no ZOL

Abbreviations: BC, breast cancer; BM, bone metastases; DTC, disseminated tumor cells; IV, intravenous; mo, month; q, every; wk, week; yr, year; ZOL, zoledronic acid; ⁺, positive.

chemotherapy for breast cancer ($N = 45$) who received monthly ZOL for 2 years experienced a significant reduction in the prevalence of DTCs at 12 and 24 months compared with baseline ($P \leq 0.001$).^{52,57} In each of these 3 studies, ZOL was generally well tolerated.^{51–54,57} The ability of ZOL to reduce DTCs in patients with breast cancer may result from anticancer synergy between endocrine therapy and ZOL, which has been demonstrated in preclinical studies.⁵⁸

Data from 3 phase III clinical trials suggest that ZOL may have anticancer benefits in the adjuvant breast cancer setting (Figure 2).^{48,59,60} In the ABCSG-12 trial, premenopausal women with early stage, endocrine-responsive breast cancer ($N = 1803$) received goserelin and tamoxifen ± ZOL or goserelin and anastrozole ± ZOL for 3 years. Analyses after a median follow-up of 48 months showed that the addition of ZOL to adjuvant endocrine therapy reduced the risk of disease progression by 36% compared with endocrine therapy alone.⁴⁸ Overall, ZOL improved disease-free survival (DFS) by 32% (hazard ratio [HR] = 0.68; 95% confidence interval [CI] = 0.51, 0.91; $P = 0.009$), decreased the risk of disease progression 36% ($P = 0.01$),⁴⁸ and produced a trend toward

improved overall survival (OS) versus no ZOL (HR = 0.66 [0.41, 1.09]; $P = 0.1$).⁴⁹ Furthermore, at 48 and 62 months' follow-up, the DFS benefits of ZOL remained significant compared with hormonal therapy alone, suggesting a long-term carryover benefit from the initial 3 years of ZOL treatment.⁴⁹

In 3 companion studies, Z-FAST ($N = 602$), ZO-FAST ($N = 1065$), and E-ZO-FAST ($N = 527$), postmenopausal women with early breast cancer receiving letrozole were randomized to receive upfront or delayed ZOL (4 mg via 15-minute infusion every 6 months) for 5 years.^{60,61} Although disease recurrence was a secondary endpoint in all 3 trials, DFS was an exploratory endpoint that none of the trials were powered to detect.^{59,60,62} Despite this, the largest of the 3 trials (ZO-FAST, $N = 1065$) showed improved DFS in patients who received upfront ZOL. After a median follow-up of 36 months, the upfront-ZOL group had a significant 41% reduction in the risk of having a DFS event compared with the delayed-ZOL group (HR = 0.588 [0.361–0.959]; log-rank $P = 0.0314$),⁵⁹ and these benefits were maintained through 60 months' follow-up (HR = 0.66 [0.44–0.97]; log-rank $P = 0.0375$).⁶³ Furthermore, an integrated 24-month analysis of the Z-FAST and ZO-FAST trials showed a 42.7% improvement in DFS in patients receiving upfront ZOL compared with delayed ZOL (HR = 0.573 [0.358–0.916] log-rank $P = 0.0183$).⁶¹ However, there was no significant difference in DFS between the upfront- and delayed-ZOL groups in the Z-FAST ($N = 602$) and E-ZO-FAST ($N = 527$) studies.⁶⁴

The AZURE trial is assessing the anticancer activity of ZOL in patients with early breast cancer. Patients with high-risk, early stage breast cancer ($N = 3360$) received anticancer therapy alone or standard therapy plus a tapered dosing schedule of ZOL (4 mg every 3–4 weeks × 6; 4 mg every 3 months × 8; 4 mg every 6 months × 5).⁶⁵ In the neoadjuvant substudy ($n = 205$) of the AZURE trial, ZOL plus neoadjuvant

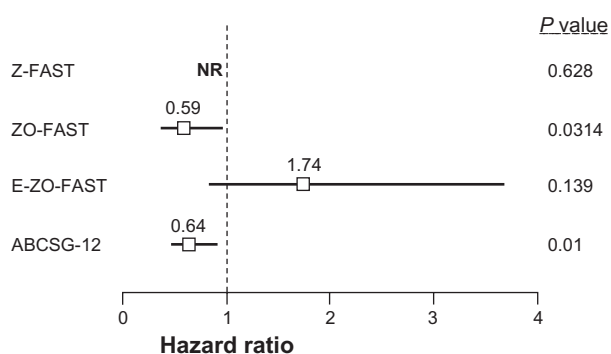


Figure 2 Forest plot of DFS outcomes in adjuvant ZOL BC trials. The ZO-FAST, E-ZO-FAST, and ABCSG-12 phase III clinical trials in patients with early BC showed that ZOL improved DFS.

Data from Gnant et al,⁴⁸ Eidtmann et al,⁵⁹ and Llombart et al.⁶⁰

Abbreviations: BC, breast cancer; DFS, disease-free survival; NR, not reported; ZOL, zoledronic acid.

anticancer therapy significantly reduced residual invasive tumor size compared with anticancer therapy alone (43%; $P = 0.006$).⁶⁶ Furthermore, patients who received ZOL had a 2-fold improvement in their pathologic complete response rates.⁶⁶ This small substudy suggests that the synergy between ZOL and chemotherapy can have a direct anticancer effect on the primary tumor.

Unlike the other adjuvant breast cancer trials described, the AZURE study was not limited to hormone-responsive breast cancer. The patient population included both premenopausal and postmenopausal women, and standard anticancer therapy included adjuvant chemotherapy as well as endocrine therapy. Overall, the trial results were negative; the adjuvant use of ZOL did not improve the primary endpoint of DFS in the overall patient population (HR = 0.98; $P = 0.79$) at a median follow-up of 59 months, although there was a nonsignificant trend toward improved OS for ZOL versus control (HR = 0.85; $P = 0.07$).⁶⁵ Interestingly, prospective protocol-defined subgroup analyses based on menopausal status showed that ZOL significantly improved DFS (HR = 0.76; $P < 0.05$) in patients who were at least 5 years postmenopausal at baseline ($n = 1041$) and OS (HR = 0.71; $P = 0.017$) when women of unknown postmenopausal status but age >60 years at baseline ($n = 1101$) were included in the subset analysis.⁶⁵ Zoledronic acid also reduced each type of recurrence both in and outside bone (HR and P value were not reported) versus control in the postmenopausal subset ($n = 1101$).⁶⁵ These results may seem inconsistent with data showing significant DFS benefits from ZOL in premenopausal women in ABCSG-12. However, the premenopausal populations in these 2 studies were markedly different. In ABCSG-12, premenopausal women underwent complete ovarian suppression with goserelin therapy plus either tamoxifen or anastrozole, which resulted in endocrine-therapy induced menopause, while most premenopausal women in the AZURE study received chemotherapy rather than endocrine therapy. The data from these large, prospective clinical trials suggest that ZOL may have anticancer activity in some patient populations, although further studies are needed to clarify which patients may receive the greatest benefit from therapy.

Discussion

Bone health in women with breast cancer is an important concern throughout the disease course. Endocrine therapy for women with early breast cancer combined with ZOL to protect bone health may also have the advantage of reducing the incidence of metastases. In women whose disease

has already spread to bone, antiresorptive therapies have established utility for delaying the onset and reducing the incidence of potentially debilitating SREs. Bisphosphonates in general and ZOL specifically have been shown to block multiple steps in the process of tumor metastasis either alone or in combination with anticancer agents.

Clinical treatment guidelines that address bone health in women with breast cancer have been developed³³ and are continually evolving as new clinical trial data become available. In addition to being a clearly established therapy for the prevention of SREs in patients with bone metastases from breast cancer, ZOL has been shown to reduce disease recurrence, improve DFS and, with longer follow-up, may also improve OS in pre- and postmenopausal women with early endocrine-responsive breast cancer. Data in this setting are promising but still investigational, as trial outcomes have varied for different patient populations.

Furthermore, guidelines for the prevention of SREs in patients with bone metastases support the use of ZOL, pamidronate, or denosumab in patients with breast cancer; ZOL or denosumab in patients with any solid tumor; and ZOL in patients with multiple myeloma. In the advanced cancer setting, prognostic indicators (eg, bone markers) of ZOL activity may ultimately allow for personalization of interventions, potentially providing a greater benefit-risk profile; however, further data are needed. Recent trials also suggest that adding ZOL to adjuvant endocrine therapy in some patient populations may protect bone health and improves clinical outcomes beyond adjuvant therapy alone. However, although ABCSG-12, the Z-/ZO-/E-ZO-FAST companion trials, and the postmenopausal subset analysis in the AZURE study have shown improved outcomes with the addition of ZOL in the adjuvant breast cancer setting, the overall results of the AZURE study were negative. The role of ZOL therapy in the adjuvant setting is evolving and ongoing studies of antiresorptive therapies (ie, ZOL and denosumab) will define this role.

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