Review Article

Zoledronic Acid Use in Cancer Patients

More Than Just Supportive Care?

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Bone is the most common site for metastasis from solid tumors, and the majority of patients will develop bone metastases during the natural course of their disease. Bisphosphonates are an effective treatment for preventing skeletal-related events in patients with bone metastases and may preserve functional independence and quality of life. Although several bisphosphonates have been investigated in patients with solid tumors, only zoledronic acid (ZOL) is approved by the US Food and Drug Administration and the European Medicines Agency for preventing skeletal-related events in patients across a broad range of solid tumors. In addition, bisphosphonates, notably ZOL, prevent cancer treatment-induced bone loss in breast and prostate cancer patients who are receiving endocrine therapy. It also has been demonstrated that ZOL directly and indirectly inhibits cancer cell growth in vitro and growth and tumorigenesis in animal model systems. These properties may produce clinically meaningful benefits. In recent clinical studies in patients with cancer, ZOL improved overall and prolonged disease-free survival. Ongoing clinical trials in patients with solid tumors will provide further insight into the potential of ZOL to prevent distant metastases and improve survival. ***Cancer* 2011;117:11–23.** © *2010 American Cancer Society.*

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During the progression of cancer, many patients will develop distant metastases, for which a common site is bone.[1] For example, an estimated 75% of patients with advanced breast cancer (BC) or prostate cancer (PC), and 40% of patients with advanced lung cancer (LC) develop bone metastases.[2,3] Without bone-targeted therapies, most patients with bone metastases will experience potentially debilitating skeletal-related events (SREs), such as pathologic fractures, spinal cord compression, the need for surgery or palliative radiotherapy to bone, or hypercalcemia of malignancy.[1] These SREs can have debilitating consequences and reduce quality of life and survival.[4] Moreover, declines in performance status resulting from SREs could preclude the receipt of chemotherapy and radiotherapy by patients with some solid tumors.[5]

Bisphosphonates, which are inhibitors of osteoclast-mediated bone resorption, currently are the standard of care for preventing SREs in patients with bone metastases.[6] Several bisphosphonates currently are approved by the US Food and Drug Administration and the European Medicines Agency for preventing SREs in patients with metastatic BC and multiple myeloma (MM). In addition, the nitrogen-containing bisphosphonate (N-BP) zoledronic acid (ZOL) has received widespread regulatory approval for patients with bone involvement from PC, LC, and the entire range of other solid tumors (OSTs).[6] In randomized phase 3 trials, ZOL (4 mg intravenously [iv] every 3 to 4 weeks [monthly]) demonstrated significant efficacy in delaying the onset and reducing the risk of SREs and in palliating bone pain, reducing analgesic use, and improving quality of life for patients with bone metastases.[7-12] Indeed, ZOL has demonstrated multiple direct and indirect anticancer activities, including the potential activation of anticancer immunomodulation.[13] Recently, ZOL has been investigated in earlier cancer settings, and emerging evidence suggests that it can provide benefits beyond bone health.[13-16] In this review article, we summarize data obtained through attendance at recent international congresses and HighWire searches for published literature on the anticancer effects of bisphosphonates.

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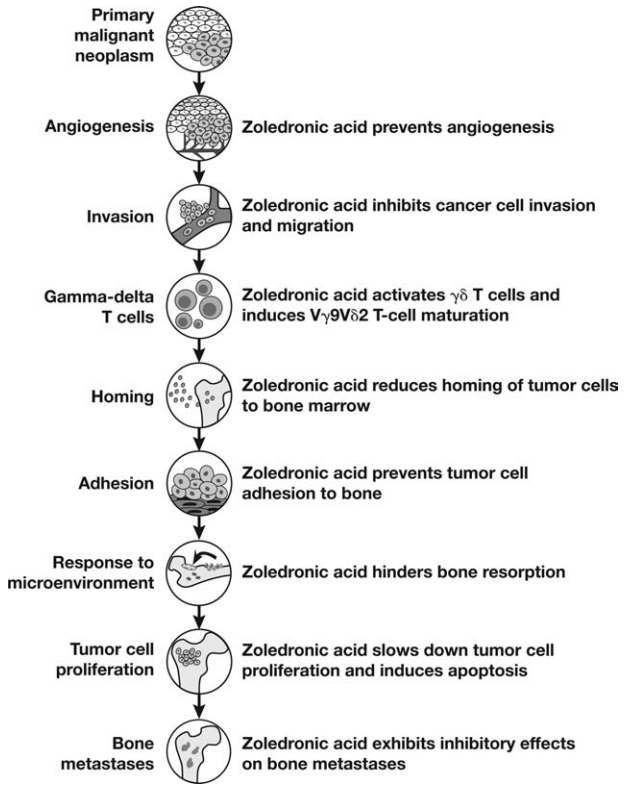

Figure 1. The antitumor profile of zoledronic acid affects tumor cells in vitro and in vivo. Zoledronic acid inhibits angiogenesis, cell invasion, homing of tumor cells to bone marrow, cell adhesion, bone resorption, and cell proliferation. Zoledronic acid also activates gamma-delta (γδ) T cells.

Preclinical Rationale for Potential Effects of Zoledronic Acid on Disease Course

In addition to their bone-protective effects, it has been demonstrated that bisphosphonates exhibit direct and indirect anticancer activity in cell cultures and animal models of human cancers. These additional bisphosphonate activities may produce clinically meaningful anticancer benefits for patients with BC.[17] In previous preclinical studies that investigated in vitro inhibition of farnesyl diphosphonate synthase (the intracellular target of N-BPs) activity, ZOL exhibited the highest activity among all evaluated bisphosphonates.[18] Preclinical data described below indicate that ZOL can inhibit cancer cell proliferation, adhesion, invasion, and angiogenesis. Moreover, ZOL can activate innate and adaptive immune responses against cancer cells, promote cancer cell apoptosis, and produce synergistic anticancer effects with concurrently or sequentially administered cancer therapies (Fig. 1). These preclinical findings provide further insight into the mechanisms of bisphosphonate action that may explain the improved disease-free survival (DFS) and recurrence-free survival observed in recent trials among patients with early BC and also provide the rationale for assessing their antitumor activity in clinical trials.

Direct Anticancer Effects

It has been demonstrated that bisphosphonates impede several of multiple steps in the metastatic process.[19] For example, in human cell lines, bisphosphonates induce tumor cell apoptosis and inhibit migration, adhesion, and invasion.[17] In 2 prostate cancer cell lines, ZOL induced apoptosis and prevented cellular adhesion to mineralized matrix.[20] Moreover, ZOL inhibited small G-proteins,[20] which suggests that ZOL may play an indirect role in chemoresistence.[21]

Bisphosphonates also have demonstrated synergistic cytotoxic or cytostatic effects when administered in combination with chemotherapy agents.[17,22-33] In human primary BC cells, concomitant exposure to ibandronate or ZOL plus cyclophosphamide combined with methotrexate and 5-fluorouracil or epirubicin combined with cyclophosphamide, paclitaxel, or docetaxel enhanced the cytostatic effects compared with chemotherapy alone.[31] In a murine model of human BC, ZOL alone reduced total tumor burden by 43% compared with placebo; moreover, ZOL plus doxycycline more effectively reduced bone tumor burden compared with doxycycline alone.[22] It is noteworthy that sequential exposure to doxorubicin (2 mg/kg) followed 24 hours later by ZOL (100 μg/kg) decreased intraosseous tumor burden in bone and increased rates of cancer cell apoptosis more than either agent alone, both agents administered simultaneously, or ZOL administered before doxorubicin.[28] Synergistic effects also have been demonstrated in the lung, prostate, and MM settings. For example, ZOL improved survival in combination with doxorubicin in mice bearing subcutaneous breast tumors compared with untreated mice.[34]

Indirect Anticancer Effects

During bone remodeling and repair, osteoclast-mediated osteolysis releases growth factors from the bone matrix that can promote the growth of cancer cells.[19] Cell lines derived from human BC and PC secrete growth factors that can regulate the bone-remodeling machinery.[19] In animal models of BC and PC, ZOL pretreatment lowered tumor burden in bone and/or impeded the development of bone metastases compared with controls.[35-38] One 5-μg ZOL dose significantly decreased bone tumor burden in a 4T1 syngeneic mouse model of metastatic BC

($P < .05$).[39] Moreover, 4 doses of ZOL (5 μg per mouse administered every 4 days) significantly increased survival compared with untreated mice ($P < .05$).[39] These data suggest that ZOL modification of the bone microenvironment can reduce bone tumor burden and growth, possibly by inhibiting the release of growth factors from bone during osteoclast-mediated osteolysis.

Survival benefits could be generated independently of anticancer effects by prevention of potentially debilitating or life-limiting fractures. For example, in a clinical study in 2127 osteoporotic patients who underwent previous surgery for hip fracture, ZOL (5 mg per year) over a median of 1.9 years significantly reduced the risk of death by 28% (141 events vs 101 events) compared with placebo (both $P \leq .01$), suggesting that prevention of fractures—or beneficial effects on other disease processes that have yet to be defined—may prolong survival in high-risk patients independent of anticancer effects.[40]

In preclinical studies, ZOL reduced tumor-associated angiogenesis.[17] For example, ZOL reduced capillary tube formation by vascular endothelial cells and prevented revascularization in a rat prostate model compared with controls.[41] These preclinical findings have translated into interesting results in pilot clinical trials. In 1 study (n = 25), pamidronate (single 90-mg infusion) reduced circulating levels of vascular endothelial growth factor (VEGF), an essential growth factor for angiogenesis, in patients with metastatic bone disease.[42] In another study in patients with bone metastases from solid tumors (N = 26) who were receiving ZOL, VEGF levels were reduced significantly after 84 days of treatment compared with placebo ($P = .014$).[43] In a second ZOL study in patients with advanced BC who received 1 ZOL dose before chemotherapy (N = 42), the majority had ≥25% lower circulating VEGF levels compared with baseline.[44] The reduction in VEGF levels was correlated significantly with prolonged time to first SRE ($P = .0002$), delayed bone disease progression ($P = .0024$), and maintained or improved performance status ($P = .0352$) compared with VEGF levels that remained unchanged.[44] The VEGF pathway is important, because increased VEGF levels are associated with a poor prognosis in patients with advanced BC.[45] Moreover, bevacizumab, an anti-VEGF antibody, has demonstrated clinical benefits in this patient population.[45]

Bisphosphonates also may reduce tumor burden indirectly by activating gamma-delta (γδ) T cells, a T-cell subset that recognizes phosphorylated antigens and possesses anticancer activities.[46,47] Nitrogen-containing bisphosphonates—alendronate, risedronate, pamidronate, and ZOL—induced the proliferation of γδ T cells isolated from healthy volunteers.[47,48] Inoculation with N-BP–activated γδ T cells reduced tumor burden compared with no treatment in an LC xenograft mouse model,[48] and pamidronate treatment significantly reduced plasma cell counts in bone marrow cultures from patients with MM.[47] In a pilot study, ZOL also produced long-term activation of effector γδ T cells in patients with early BC (N = 23).[49] Further studies are needed to determine how best to apply the ZOL-mediated activation of γδ T cells to clinical practices.

The bone marrow has been implicated as a potential reservoir for "dormant" cancer stem cells that may be the source of disease recurrence or relapse.[50] In 4 small trials in patients with BC, adjuvant ZOL reduced the numbers of disseminated tumor cells (DTCs) in the bone marrow compared with baseline.[51-55] Patients with early BC and DTCs in the bone marrow (N = 45) who received endocrine therapy plus ZOL (4 mg per month iv for up to 2 years) had significant decreases in bone marrow DTCs at the 1-year follow-up ($P = .0006$) and the 2-year follow-up ($P = .0026$) compared with baseline.[52] In a subsequent randomized study among patients with early BC and DTCs in the bone marrow (N = 96), adding ZOL (4 mg per month iv for up to 2 years) to adjuvant therapy resulted in a higher proportion of patients with negative bone marrow assessments compared with patients who received endocrine therapy alone (66.7% vs 35.1%, respectively; $P = .009$).[54] In a larger, matched-pair study (N = 172) among patients with DTCs in bone marrow, patients who received adjuvant chemotherapy plus ZOL (4 mg per month iv) for 6 months were more likely to be free of DTCs at subsequent assessment compared with patients who received chemotherapy alone ($P = .099$ for between-group comparison).[53] However, the science of DTC research still is evolving, and it is unclear whether DTC numbers or specific types of DTCs (which may have different sensitivities to therapy) are important for disease recurrence. Nonetheless, the results from these studies suggest that ZOL may indirectly prolong survival by reducing the viability or proliferation of the DTCs within the bone marrow that could be the source for disease recurrence.

Clinical Evidence for Survival Benefits From Zoledronic Acid in Advanced Cancer

The first evidence that ZOL may beneficially affect disease-related outcomes, such as survival, emerged from the

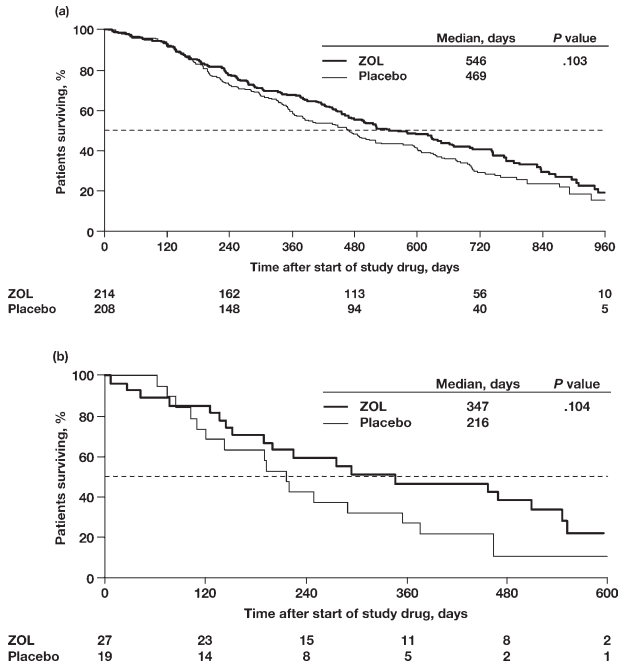

Figure 2. Kaplan-Meier estimates of survival for zoledronic acid (ZOL) versus placebo are shown in patients with (a) hormone-refractory prostate cancer or (b) renal cell carcinoma. Reprinted from Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumor effects. *Cancer Treat Rev.* 2008;34:183-192.[4] Copyright 2008, with permission from Elsevier.

secondary endpoints of the phase 3 registration studies in patients with malignant bone disease.[4,11,56,57] In patients with bone metastases from hormone-refractory PC (HRPC) (also often referred to as castration-resistant PC; n = 422), ZOL (4 mg) produced trends toward improved overall survival (OS) compared with placebo ($P = .103$) (Fig. 2a).[4,11,57] Similarly, exploratory analyses of the subset of patients with renal cell carcinoma (RCC) (n = 46) in a trial of patients with bone metastases from LC/OST revealed a trend toward prolonged survival with ZOL ($P = .104$) (Fig. 2b).[4]

Possible factors contributing to the potential survival benefits of ZOL in patients with bone metastases were evaluated. Exploratory analyses of the ZOL phase 3 trial database revealed that pathologic fractures significantly increased the risk of death by 29% in patients who had HRPC ($P = .04$) and by 52% in patients who had BC compared with patients who had no fractures ($P < .01$).[58] Therefore, ZOL may indirectly prolong survival in patients with bone metastases through preventing life-limiting SREs, such as pathologic fractures. For example, in patients with bone metastases from HRPC, ZOL reduced the incidence of pathologic fractures by a relative 32% (17% vs 25% for placebo) and prolonged the time to first pathologic fracture by 6.5 months compared with placebo (both $P = .02$).[59,60] These findings suggest that preventing or delaying the onset of pathologic fractures potentially could provide survival benefits for patients with bone involvement from their cancer. However, it is likely that additional mechanisms contribute to these potential OS benefits.

Anticancer Effects in the Advanced Disease Setting

Zoledronic acid has demonstrated progression-free survival and OS benefits in some studies among patients with bone metastases. In a randomized, open-label pilot study of patients with recurrent solid tumors and no evidence of bone metastases (N = 40), ZOL (4 mg per month iv) resulted in significantly prolonged bone metastases–free survival at 12 months and 18 months compared with no ZOL ($P < .0005$ and $P = .0002$, respectively).[61] Conversely, in a study among patients with earlier stage, smouldering myeloma (N = 163), ZOL reportedly did not have a significant effect on disease course. Patients with this stage of myeloma, however, usually are asymptomatic and have a relatively low risk of SREs and disease progression; typically, they are not treated until they progress to symptomatic MM. In addition, ZOL was administered for only 12 months, and it is possible that a longer duration of treatment may have been more effective.[62] Indeed, in a pilot study of patients who were receiving initial chemotherapy for MM (N = 94), ZOL (4 mg per month iv) significantly improved the 5-year OS rate from 46% to 80% compared with chemotherapy alone ($P < .01$).[63] Similarly, a pilot study in patients with bone metastases from bladder cancer (N = 40) demonstrated that ZOL (4 mg per month iv for 6 months) significantly reduced the risk of SRE by 58% ($P = .008$), reduced pain scores by 1.42 units versus placebo ($P = .015$), and improved the 1-year OS rate 6-fold ($P = .02$) versus placebo.[64] In addition, patients with bone metastases from LC (N = 144) who received standard chemotherapy and ZOL (4 mg iv every 21 to 28 days for 1 year) for bone pain had longer median survival compared with patients who received standard chemotherapy but not ZOL (578 days vs 384 days, respectively; $P < .001$).[65] Additional therapies may improve survival further. For example, among patients with metastatic HRPC who received androgen blockade (N = 38), combining ZOL (4 mg iv every 4 weeks) with dexamethasone (4 mg daily for up to

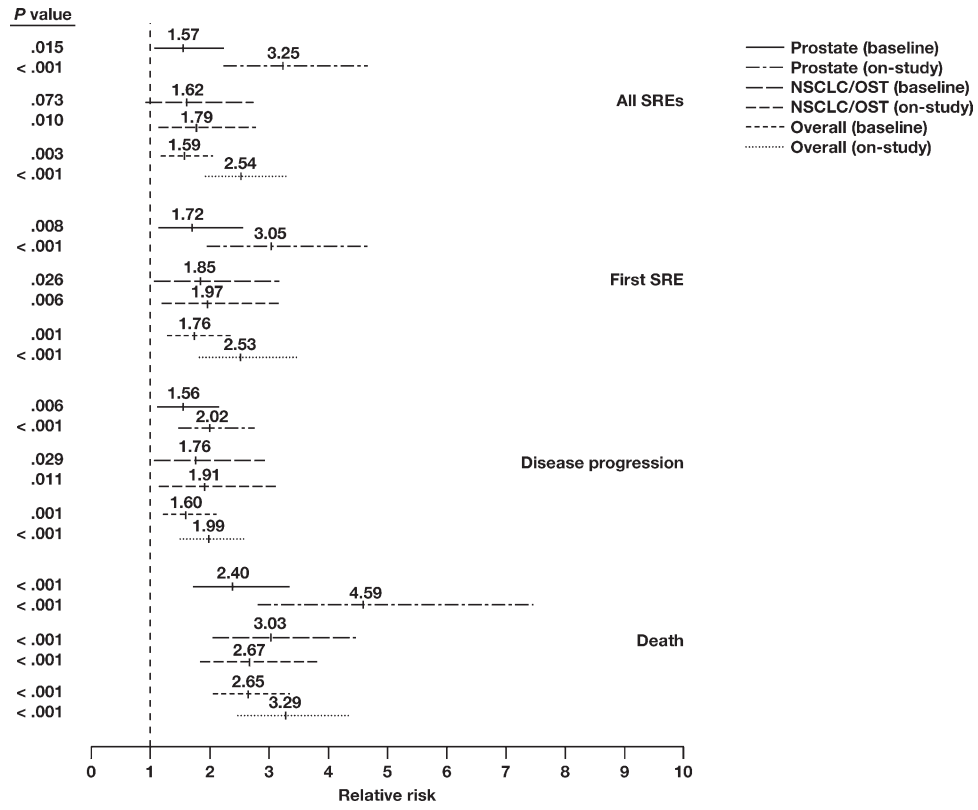

Figure 3. Forest plot of relative risks of negative outcomes are shown from a dichotomous N-telopeptide of type I collagen (NTX) analysis using creatinine cutoff values of 100 nmol/mmol. The increased risks for patients with prostate cancer, nonsmall cell lung cancer (NSCLC)/other solid tumors (OST), and overall are shown for the occurrence of all skeletal-related events (SREs) and for the time to first SRE, disease progression, and death. Reprinted from Brown JE, Cook RJ, Major P et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst*. 2005;97:59-69.[68] By permission of Oxford University Press.

1 month, then gradually reduced to 1 mg daily by the fourth month) and octreotide (20 mg intramuscularly every 28 days) significantly improved median progression-free survival ($P < .0001$) and OS ($P = .0027$) compared with ZOL alone.[66] Taken together, the results from these studies suggest that ZOL may have benefits beyond preventing SREs for patients with advanced cancers, even before the development of bone metastases.

Bone Marker Effects and Survival in Advanced Cancer Patients

The bone microenvironment plays a key role in fostering tumor growth, and interactions between tumor and bone can result in increased bone resorption. Ongoing bone turnover rates can be monitored in patients by using biochemical markers of bone metabolism, such as N-telopeptide of type I collagen (NTX), which is released into the bloodstream during osteoclast-mediated bone resorption and excreted in the urine.[67] Retrospective analyses from the phase 3 trials of ZOL in patients with metastatic solid tumors revealed that approximately 66% of patients had baseline urinary NTX levels at or above the normal threshold for young healthy adults (50 nmol/mmol creatinine).[67] In exploratory analyses among patients with bone metastases from HRPC, nonsmall cell LC (NSCLC), or OSTs, markedly elevated NTX levels at baseline ($\geq$100 nmol/mmol creatinine) significantly increased the risk of SRE onset, disease progression, and death ($P \leq .029$ for all) compared with patients who had baseline NTX levels $<$100 nmol/mmol creatinine (Fig. 3).[68] Therefore, by inhibiting malignant osteolysis, bisphosphonates may have indirect effects on the disease course.

Treatment with ZOL results in the normalization of elevated NTX levels in the majority of patients with bone metastases from solid tumors and may provide a survival benefit.[56,69,70] A retrospective analysis of the ZOL phase 3 trial database demonstrated that ZOL normalized elevated baseline NTX levels ($\geq$64 nmol/mmol creatinine)

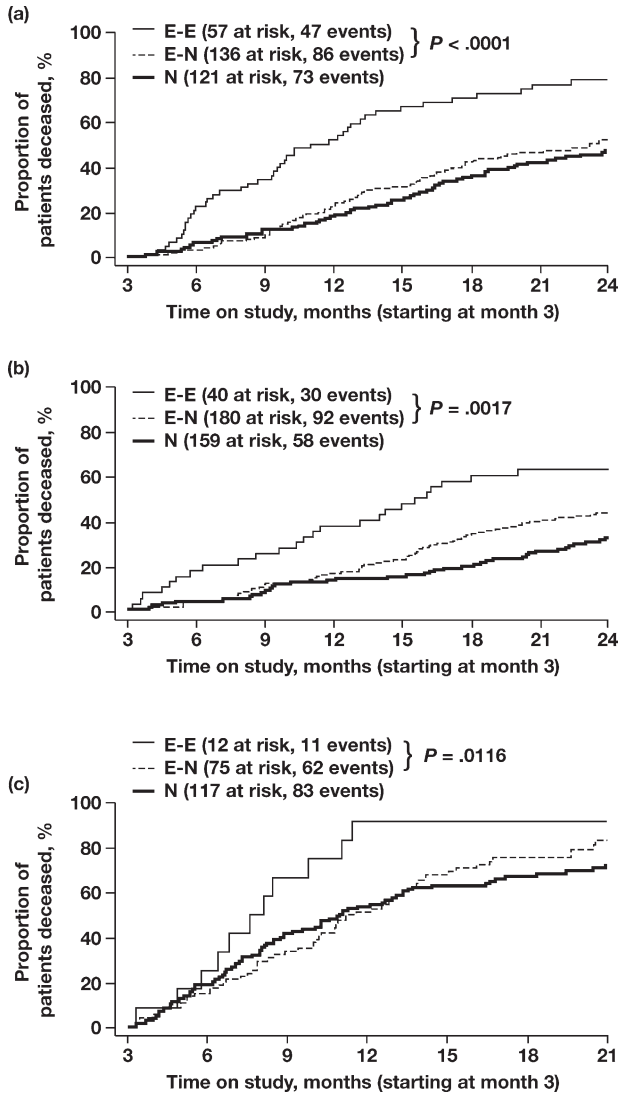

Figure 4. Kaplan-Meier estimates of (a) prostate cancer survival, (b) breast cancer survival, and (c) lung cancer survival are shown by baseline and 3-month N-telopeptide of type I collagen (NTX) levels. E-E indicates patients with persistently elevated NTX; E-N, patients with elevated baseline NTX who had normalized by 3 months; N, patients with normal baseline NTX. Adapted with permission from Lipton A, Cook R, Saad F et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. *Cancer*. 2008;113:193-201.[56]

within 3 months in approximately 81% of patients with BC, 70% of patients with HRPC, and 81% of patients with NSCLC/OST.[56] In patients with elevated baseline NTX levels, NTX normalization within 3 months of initiating ZOL was correlated with improved OS compared with patients who had persistently elevated NTX levels (Fig. 4).[56] Indeed, in a subsequent meta-analysis of placebo-controlled trials in patients with HRPC, NSCLC, OST, or BC and elevated baseline NTX levels ($\geq$100 nmol/mmol creatinine), ZOL treatment reduced the risk of death by 26% compared with the placebo group ($P = .006$).[71] This result probably is associated with a decrease in bone turnover markers and a delay in onset and reduction in incidence of SREs that are either potentially life-limiting or that prevent treatment of the underlying cancer, rather than a direct anticancer effect.

Consistent with results from that meta-analysis, significant survival benefits were revealed in patients with metastatic NSCLC who had elevated baseline NTX levels. In a ZOL trial among patients with NSCLC/OST, ZOL treatment reduced the risk of death by 35% compared with placebo ($P = .024$) in a multivariate model that controlled for the effects of all other significant covariates.[69] Ongoing studies will help define the prognostic value of bone turnover markers during antiresorptive therapy.

Clinical Evidence for Survival Benefits From Zoledronic Acid in Early Cancer

Bisphosphonates are an integral component of care for patients with postmenopausal osteoporosis, and are emerging as a viable therapy for cancer treatment-induced bone loss (CTIBL). Breast cancer therapies, such as chemotherapy, ovarian oblation/suppression, and aromatase inhibitor therapy, are associated with rapid bone loss and increased risk of fractures.[72] Zoledronic acid has demonstrated efficacy in preventing CTIBL and improving bone mineral density (BMD) above baseline in premenopausal and postmenopausal women with early BC who are receiving adjuvant endocrine therapy.[73-79] In addition to its bone-protective benefits, recent large, phase 3 studies demonstrated that ZOL can prolong DFS compared with standard therapy alone.[14,16,80]

Completed Trials and Interim Reports

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 12 (ABCSG-12) is a large, randomized, phase 3 trial that compared the efficacy of endocrine therapy with and without ZOL in 1803 premenopausal women with early stage BC.[14] Patients were randomized to receive monthly goserelin (3.6 mg every 28 days) and tamoxifen (20 mg daily) or anastrozole (1 mg daily) with or without ZOL (4 mg every 6 months) for 3 years. After a median follow-up of 48 months, there were no significant differences in efficacy between anastrozole and tamoxifen on the primary endpoint (DFS). However, ZOL produced a 36% relative reduction in the risk of disease

progression (hazard ratio [HR], 0.64; log-rank $P = .01$) and a 35% relative reduction in disease recurrence (HR, 0.65; log-rank $P = .01$) compared with endocrine therapy alone.[14] Zoledronic acid also produced a trend toward improved OS (HR, 0.60; 40% relative risk reduction; log-rank $P = .10$) and the investigational endpoint of bone metastases–free survival (HR, 0.68; 32% relative risk reduction; $P = .22$) versus endocrine therapy alone. Reductions in disease recurrence with ZOL were not limited to sites in bone. Decreased incidences of metastases to bone and other sites (locoregional and visceral) compared with endocrine therapy alone were reported.[14] Potential mechanisms for the study observations, including direct and indirect effects of ZOL on incidence of metastases, are discussed below. Endocrine therapy plus ZOL generally was well tolerated, and adverse events were consistent with the established safety profiles of each agent. No renal toxicity or osteonecrosis of the jaw was noted in this study.[14]

The ZOMETA-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST, and E-ZO-FAST) are 3 parallel studies in postmenopausal women with endocrine-responsive, early BC (N = 2189) who were randomized to receive letrozole (2.5 mg per day orally) and either upfront ZOL (4 mg iv every 6 months) or delayed ZOL (initiated after a postbaseline T-score <-2.0, a nontraumatic fracture, or a radiographically detected fracture at 3 years) for 5 years.[15,74,80-82] In each of these trials, upfront ZOL met its primary endpoint of BMD preservation versus delayed ZOL.[74,80,82] Integrated analyses of Z-FAST (N = 602) and ZO-FAST (N = 1065) at 24 months revealed that upfront ZOL reduced disease recurrence compared with delayed ZOL despite 19% of patients in the delayed arm initiating ZOL (3.6% vs 5.5%, respectively, developed a recurrence; HR, 0.573; log-rank $P = .0183$).[15] These differences were maintained in long-term follow-up of Z-FAST (at 61 months' follow-up; HR, 0.80; P value not significant) and ZO-FAST (at 48 months' follow-up; HR, 0.59; $P = .0175$).[83] However, in the smallest and most geographically diverse of these studies (E-ZO-FAST; N = 527), fewer patients experienced disease recurrence by 36 months in the delayed ZOL arm versus the upfront ZOL arm (11 patients vs 18 patients, respectively).[83] Regardless, these results overall suggest that early ZOL treatment may have clinical benefits beyond bone health for postmenopausal patients with early BC.

In the AZURE trial, women with stage II/III BC (N = 3360) who were receiving adjuvant chemotherapy and/or endocrine therapy were randomized to receive either ZOL (4 mg every month $\times$ 6, then every 3 months $\times$ 8, then every 6 months $\times$ 5) or no ZOL.[17,84] This 5-year trial is ongoing; however, an early exploratory analysis has been reported. In a subset analysis of patients who received neoadjuvant chemotherapy (n = 205), adding ZOL reduced the mean residual invasive tumor size at surgery by 33% compared with chemotherapy alone (28.2 mm vs 42.4 mm, respectively; $P = .002$).[16] Moreover, the pathologic complete response rate (breast and axilla) was almost 2-fold higher among ZOL-treated patients compared with those who received neoadjuvant chemotherapy alone ($P = .03$), and fewer ZOL-treated patients required mastectomies compared with patients who received neoadjuvant chemotherapy alone (65.3% vs 77.9%, respectively).[16] These results suggest that adding ZOL to neoadjuvant chemotherapy may provide clinical benefits to patients with BC beyond those of standard therapy alone, perhaps because of the inherent antitumor properties of bisphosphonates or anticancer synergy of ZOL with cytotoxic agents, both of which have been demonstrated in preclinical studies.[17]

Ongoing Studies

Breast cancer

Investigations with the first-generation bisphosphonate clodronate (a non–N-BP) suggested that this class of agents could delay the course of BC progression.[85-88] However, results were inconsistent between trials, and, in a recent meta-analysis, no significant difference in survival outcome was reported between clodronate and placebo.[89] The large National Surgical Adjuvant Breast and Bowel Project (NSABP) NSABP-34 trial, which has completed accrual, randomized approximately 3350 patients with stage I/II BC to receive 3 years of either clodronate (1600 mg daily) or placebo.[17] That trial is assessing DFS as the primary endpoint and may yield a definitive answer regarding the clinical benefits of clodronate in the adjuvant setting in the near future. Several ongoing studies are assessing the potential of more active N-BPs to prevent bone metastases and improve DFS in the adjuvant setting (Table 1).[90-102] The ICE and GAIN trials will assess the efficacy of ibandronate in early BC patients.[90-92] In addition, the Southwest Oncology Group (SWOG) SWOG 0307 study is examining patients who are receiving standard adjuvant therapy plus oral ibandronate, oral clodronate, or ZOL for BC.[96] The efficacy of ZOL also is being evaluated in ongoing studies in the early BC setting (the ANZAC, NATAN, and SUCCESS trials).[93-95]

Table 1. Ongoing Clinical Trials With Bisphosphonates

Trial Name	Reference(s)	Patients	Treatment Arms	Primary Endpoint
ICE	German Breast Group 2009[90,91]	1400 BC patients (stage II, III)	IBN (50 mg/d or 6 mg IV q4wk)±CAP	Relapse at 2 y
GAIN	German Breast Group 2009 Paterson[91,92]	3000 BC patients (lymph node positive)	EPI+PAC+CYC±IBN; EPI+CYC+PAC+CAP±IBN	DFS at 2 y
ANZAC	Sheffield Teaching Hospitals NHS Foundation Trust 2009[93]	44 BC patients	FEC+DOC±ZOL (4 mg IV) before surgical resection	Tumor apoptotic index
NATAN	German Breast Group 2009[94]	654 BC patients	Standard therapy±ZOL (4 mg IV q1mo; q3mo; q6mo)	EFS at 5 y
SUCCESS	The SUCCESS Study Group 2009[95]	3754 BC patients (stage I, II, IIIA)	FEC+DOC then endocrine therapy+ZOL for 2 y or 5 y; FEC+DOC+GEM then endocrine therapy+ZOL for 2 y or 5 y	DFS at 5 y
SWOG 0307	Southwest Oncology Group 2009[96]	5400 BC patients (stage I, II, IIIA)	ZOL (4 mg q1mo; q3mo); CLO (1600 mg/d); IBN (50 mg/d)	DFS and OS up to 10 y
ZEUS	European Association of Urology 2009[97]	1498 PC patients (high-risk, early)	Standard therapy±ZOL (4 mg IV q3mo)	EFS at 4 y
RADAR	Trans-Tasman Radiation Oncology Group 2009[98]	1071 PC (stage T2b-4)	ADT for 6 mo or 18 mo±ZOL (4 mg IV q3mo)	PSA-RFS at 18 mo
STAMPEDE	Medical Research Council 2009, James 2009[99,100]	3300 PC patients (high risk)	ADT and 1) no additional therapy; 2) DOC (q3wk); 3) celecoxib (BID); 4) ZOL (q3wk; q4wk); 5) DOC+ZOL; 6) celecoxib+ZOL	FFS and OS (multiple phases)
Study 2419	Novartis 2009[101]	446 NSCLC patients (stage IIIA or IIIB)	ZOL (4 mg IV q1mo)	TTP
DAZZLE	Gleneagles Hospital 2009[102]	53 MM patients	ZOL+DEX+THAL	Disease progression at 6 mo
MMIX	—	1960 MM patients	Various treatment regimens+ZOL or CLO	PFS and OS

BC indicates breast cancer; IBN, ibandronate; IV, intravenous; q4wk, every 4 weeks; CAP, capecitabine; EPI, epirubicin; PAC, paclitaxel; CYC, cyclophosphamide; ±, with or without; DFS, disease-free survival; NHS, National Health Service; FEC, combined 5-flurouracil, epirubicin, and cyclophosphamide; DOC, docetaxel; ZOL, zoledronic acid; EFS, event-free survival; q1mo, monthly; q3mo, every 3 months; GEM, gemcitabine; OS, overall survival; CLO, clodronate; PC, prostate cancer; ADT, androgen-deprivation therapy; PSA-RFS, prostate-specific antigen recurrence-free survival; BID, twice daily; FFS, failure-free survival; NSCLC, nonsmall cell lung cancer; TTP, time to progression; MM, multiple myeloma; DEX, dexamethasone; THAL, thalidomide.

Other cancers

Similar to CTIBL in patients with BC, adjuvant therapies for PC can lead to bone loss and increased fracture risk. Moreover, the mechanisms underlying potential anticancer effects are similar in the early BC and PC settings.[13] Two placebo-controlled trials of clodronate (2080 mg daily) recently reported 10-year survival rates in men with PC with or without metastatic disease (N = 311 and 508, respectively).[103] Clodronate was associated with an OS benefit among men with metastatic disease compared with placebo (HR, 0.77; $P = .032$). However, among men without metastatic disease, there was no evidence of a survival benefit with clodronate compared with placebo (HR, 1.12; $P = .94$). Ongoing trials are evaluating the efficacy of ZOL (the only approved bisphosphonate in PC) for improving clinical outcomes, such as survival, in >7000 men with early PC who are receiving androgen-deprivation therapy. The survival benefit of ZOL is being assessed as the primary endpoint in the ZEUS, RADAR, and STAMPEDE trials and as secondary endpoints in the TRAPEZE, ASAP, and Cancer and Leukemia Group B (CALGB) 90202 trials.[97-100] Potential anticancer effects of ZOL also are being assessed in patients with LC (Study 2419) and MM (the DAZZLE and MMIX studies).[101,102] The overall clinical trial program assessing the anticancer effects of ZOL in different tumor types involves approximately 25,000 patients in >15 trials. These ongoing trials will provide insight into the potential anticancer activities of bisphosphonates and may identify new treatment modalities that improve clinical outcomes.

In conclusion, in addition to the established efficacy of bisphosphonates for delaying the onset and reducing the risk of SREs in patients with malignant bone disease, emerging data suggest that ZOL may delay disease progression and prolong survival in some patients and settings. Preclinical evidence and data from emerging pilot and large phase 3 studies strongly suggest that bisphosphonates have anticancer and antimetastatic activities. Moreover, emerging data suggest that concomitant treatment with standard therapy and ZOL may substantially improve survival outcomes beyond those achieved with standard therapy alone. To date, the majority of clinical trials assessing the antitumor activity of ZOL have been performed in patients with early BC; however, several ongoing trials are assessing the benefits of ZOL in other early cancer settings. Additional prospective clinical trials are assessing the potential survival benefits of ZOL and the evolving role of ZOL in managing patients in later disease stages. It can be anticipated that the results from these studies may expand the role of bisphosphonates in the early and advanced cancer settings.

CONFLICT OF INTEREST DISCLOSURES

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