REVIEWS

Effects of Bone-Targeted Agents on Cancer Progression and Mortality

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Bone-targeted treatments with bisphosphonates and denosumab, which reduce bone resorption, are known to reduce the risk of skeletal complications and prevent treatment-induced bone loss in patients with malignant bone disease. Additionally, these drugs may modify the course of bone destruction via inhibitory effects on the "vicious cycle" of growth factor and cytokine signaling between tumor and bone cells within the bone marrow microenvironment. Effects of the drugs on the stem cell niche, direct effects on the cancer cells, and immune modulation may also contribute. In early-stage (stages I, II, and III) breast cancer, treatment with the bisphosphonate zoledronic acid has shown improvements in disease-free and overall survival. Improved survival was particularly notable in women with established menopause at diagnosis and in premenopausal women with endocrine-responsive disease who received treatment with goserelin, which suppresses ovarian function by inhibiting the production of ovarian hormones. Additionally, in castrate-resistant prostate cancer, treatment with denosumab delays the development of bone metastases. These results strongly support the adjuvant use of bone-targeted treatments but suggest that reproductive hormones are an important treatment modifier to take into account. In advanced-stage (stage IV, ie, metastatic) cancers, survival benefits have been observed in patients with multiple myeloma and in patients with other solid tumors with rapid rates of bone destruction who received treatment with zoledronic acid. Here, we have critically reviewed the increasing evidence to support a disease-modifying effect of bone-targeted treatment and discussed the impact on clinical management.

Traditionally, bone-targeted agents have been used as a supplementary therapy to prevent or reduce the incidence of skeletal-related events (SREs) in patients with malignant bone disease. However, there may be a greater role for the use of these agents than has previously been considered. A recent body of evidence suggests that they may act as antitumor agents (1), able to delay disease progression and prolong survival in multiple myeloma (2) and in solid tumors such as breast (3) and prostate cancers (4).

Bone disease contributes substantially to morbidity and mortality in patients with cancer. Approximately 70% of patients with myeloma have overt lytic metastases at diagnosis, and approximately 60% of patients report a pathological bone fracture over the course of their disease (5). Results from the Medical Research Council (MRC) Myeloma IX trial show that patients with myeloma with bone disease at diagnosis have a statistically significantly shorter overall survival (OS) compared with patients without bone disease—a shorter survival from relapse being the main contributor to this effect (median survival = 12.2 vs 23.4 months) (2). Similarly, advanced-stage (stage IV, ie, metastatic) breast cancer is associated with a heavy burden of skeletal disease, with potentially debilitating or life-limiting SREs (6,7).

Increasing knowledge about the interplay between disseminated tumor cells (DTCs), the bone marrow, and associated growth factors has identified that the complex interactions present in the bone marrow microenvironment present opportunities for therapeutic targeting (8). As a result, modification of the microenvironment surrounding cancer cells is emerging as an important anticancer strategy (9).

Studies of the biology underlying bone metastasis support the notion that in solid tumors and multiple myeloma, increased osteoclastogenesis or the process of bone resorption is both a consequence and a necessity for tumor growth and clonal expansion (10,11). The bone marrow microenvironment is a rich source of bone-derived growth factors including transforming growth factor-beta (TGF-β) and insulin-like growth factor (IGF) that are released during osteolysis (12). These factors support cancer cell growth and the formation of bone lesions and may also activate DTCs from a dormant to a proliferative state, seeding relapses in the bone after treatment. The bone marrow microenvironment is also a reservoir of immune cells, and there may be an important contribution of T cells in the regulation of tumor cell growth in bone (13).

Multiple myeloma is currently viewed as a prototypical disease model for studying tumor–microenvironment interactions (11,14). Myeloma cells have been shown to induce changes in several cell types that are intimately involved in the induction of bone lesions,

including bone marrow stem cells, bone marrow endothelial cells, immune cells, and osteoblasts and osteoclasts that control the bone formation and resorption equilibrium (11). The induced changes, in turn, provide myeloma cells with a supportive stromal environment, access to vascular networks, and locally produced growth factors and cytokines (11), all favoring continued growth and survival. Cell adhesion-mediated drug resistance, a feature of the myeloma cell interaction with osteoclasts, could also be responsible for maintaining myeloma stem cells within a stromal cell niche in the bone marrow, mediating chemoresistance and subsequent disease relapse (10). Additionally, genetic lesions associated with subgroups of myeloma have been identified, which increase the risk of bone disease through increasing myeloma cell proliferation and adhesion to stromal cells (15).

Preclinical Evidence for Disease-Modifying Effects in Solid Tumors

Bisphosphonates (BPs) are the current standard of care for the prevention and treatment of malignant bone disease (16,17). BPs naturally bind to mineralized surfaces such as bone and inhibit osteoclast-mediated bone resorption. The second-generation nitrogen-containing BPs (N-BPs) (eg, zoledronic acid, pamidronate) have been proven more effective at reducing SREs compared with the first-generation BP compounds (eg, clodronate) (17). There is extensive preclinical evidence suggesting that N-BPs exhibit antitumor effects in addition to their therapeutic activity in preserving bone tissue. The underlying inhibitory mechanisms of N-BPs against tumor cells are primarily through the blockade of the enzyme farnesyl diphosphatase (FPP) synthase in the mevalonate pathway. In vitro, the N-BPs inhibit tumor cell adhesion, migration, invasion, and proliferation and induce cell death in a wide range of cell lines, whereas in vivo, the reductions in skeletal tumor burden in a variety of mouse models of bone metastasis, including intracardiac injection of MDA-MB-231 cells and tail vein administration of MDA-BO2 cells (both human breast cancer cell lines), have been attributed primarily to their antiresorptive activity (18). For example, by inhibiting bone resorption, zoledronic acid deprives tumor cells of bone-derived growth factors (eg, TGF-β) that are required for the seeding and growth of tumor cells in the bone marrow (19). N-BPs might also alter the retention of calcium-sensing receptor-expressing tumor cells in the bone marrow by inhibiting the release of ionic calcium from bone mineral (20). In soft tissue mouse tumors and metastases, N-BPs may exert anticancer activity by interacting with monocytes, macrophages, and tumor cells. For example, zoledronic acid inhibits breast cancer cell invasion in visceral organs (lung, liver) in vivo (21,22). N-BPs also synergize with cytotoxic drugs such as doxorubicin to prevent tumor cell growth and survival in vivo (18). They also reduce tumor-associated angiogenesis in different mouse models of cancer (myeloma, melanoma, and breast, ovarian, and cervical carcinomas) (21,23).

CD11b (also known as integrin, alpha M [complement component 3 receptor 3 subunit]) and vascular endothelial growth factor (VEGF; also known as VEGFA) are known to have key roles in cell adhesion (24) and angiogenesis, respectively (25).

In some models, N-BP treatment of tumor xenograft-bearing mice induced a profound reduction in CD11b-positive (CD11b+) macrophages infiltrating mammary or cervical carcinoma lesions, which was accompanied by decreased VEGF and matrix metalloproteinase (MMP)-9 (also known as matrix metallopeptidase 9) levels in the tumor microenvironment (26). This may be explained by the fact that MMP-9 produced by CD11b+ macrophages regulates the mobilization of VEGF from the extracellular matrix. Interestingly, the bone marrow is a reservoir for proangiogenic CD11b+ myelomonocytic cells that contribute to the vascularization of primary tumors (27). N-BPs could therefore inhibit tumor-associated angiogenesis by blocking the recruitment of bone marrow-derived myeloid cells to the site of tumors.

Recent in vivo data using a panel of human breast cancer cell lines injected into nonobese diabetic severe combined immunodeficient (NOD/SCID) mice indicate that N-BPs stimulate the expansion of Vγ9Vδ2 T cells, a subset of human T cells with antitumor activity (28,29). For example, upon adoptive transfer into immunodeficient mice, purified human Vγ9Vδ2 T cells given together with alendronate (a drug given to postmenopausal women for the treatment of osteoporosis) plus the cytokine interleukin-2 showed a statistically significantly prolonged survival of mice bearing human melanoma or pancreatic carcinoma cells (28). Similarly, treatment with zoledronic acid enhanced Vγ9Vδ2 T-cell cytotoxicity in experimental models of chronic myelogenous leukemia and breast, lung, and bladder carcinoma (28,29). Indeed, as a result of the inhibition of FPP sythase in the mevalonate pathway, zoledronic acid induces the intracellular accumulation and secretion of the ATP analogues isopentenyl pyrophosphate (IPP) and 1-adenosin-5′-yl ester 3-(3-methylbut-3-enyl) ester triphosphoric acid (ApppI) in tumor cells in vitro and in vivo, promoting chemotaxis of Vγ9Vδ2 T cells to tumors and triggering their destruction (29). Moreover, zoledronic acid enhances direct natural killer cytotoxicity against tumor cells (30). Thus, there is a growing interest and a substantive dataset to support the use of N-BPs for cancer immunotherapy.

The Antimyeloma Effects of Bone-Targeted Agents

There is strong preclinical evidence from various mouse models of multiple myeloma using injection of primary myeloma cells or the 5T2 multiple myeloma cell line to suggest that N-BPs such as zoledronic acid have anticancer activity including inhibition of angiogenesis, enhancement of antitumor immune responses, and direct or indirect modulation of the proliferation and survival of myeloma cells (19,28,30). This has been confirmed by a number of clinical trials showing that bisphosphonates improve survival and extend the time to progression in myeloma patients (2,31–33). These findings further support the notion that the interaction between myeloma cells and the surrounding bone marrow microenvironment (Figure 1) constitutes an important factor that needs to be taken into account in the development of novel therapeutic strategies.

In vivo, N-BPs may also affect progression of myeloma by blocking the release of cytokines and growth factors from the
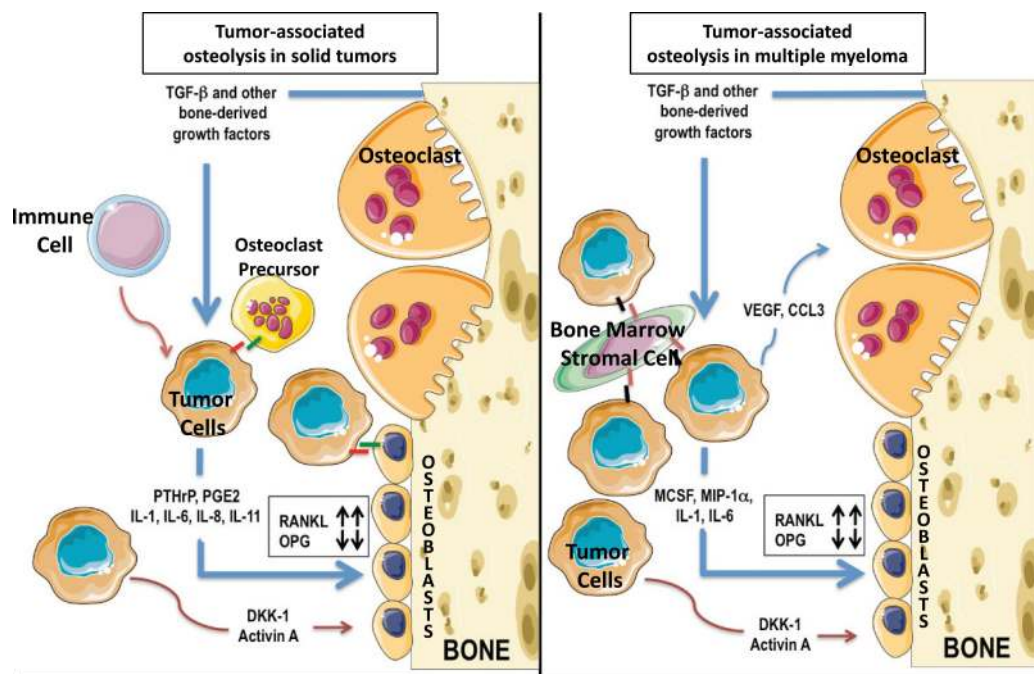
Figure 1. Mechanisms of tumor-associated osteolysis in solid tumors and multiple myeloma. Tumor cells secrete different factors (such as PTHrP, PGE2, IL-1, IL-6, IL-8, and IL-11, M-CSF and MIP-1α) that stimulate osteoclast differentiation and maturation through the activation of the RANKL/RANK pathway (by increasing the ratio of RANKL to OPG) (8,11). In solid tumors, metastatic cancer cells also directly interact with osteoclast precursors, promoting osteoclastogenesis through activation of the Jagged1/Notch signaling pathway. Moreover, tumor cells secrete components (DKK-1, and activin A) that inhibit osteoblast differentiation. This leads to enhanced bone destruction and, as a consequence, to the release of bone derived-factors (TGF-β) that stimulate tumor growth. There is therefore a "vicious cycle" whereby tumor cells stimulate osteoclast-mediated bone resorption, and growth factors released from resorbed bone stimulate tumor growth. Bone marrow stromal cells and immune cells are recruited to tumors and regulate tumor growth in bone. The drawings were produced using Servier Medical Art (www.servier.com). CCL3 = chemokine C-C motif ligand 3; DKK-1 = dickkopf-1; IL = interleukin; M-CSF = macrophage-colony stimulating factor; OPG = osteoprotegerin; PGE2 = prostaglandin E2; PTHrP = parathyroid hormone-related peptide; RANK = receptor activator of nuclear factor kB; RANKL = RANK ligand; TGF-β = transforming growth factor-β; VEGF = vascular endothelial growth factor.

bone matrix, thereby breaking the "vicious cycle" of bone destruction and cancer growth (34). In addition, the anticancer effects of BPs have been demonstrated to have synergy with agents that are used in the treatment of myeloma, including dexamethasone, thalidomide, and bortezomib (35–37). Preclinical mouse models of myeloma indicate that the antimyeloma effect of N-BPs may be mediated via the inhibition of protein prenylation and consequent inhibition of the RAS-RAF-MAPK pathway (38), a mechanism of action not shared by non-N-BPs. Based on the preclinical theory and promising early results in patients, the MRC Myeloma IX trial, a large randomized trial was conducted to evaluate the role of BPs in 1960 patients newly diagnosed with myeloma and receiving either intensive (ie, high dose) chemotherapy with stem cell rescue or nonintensive (ie, standard dose) chemotherapy regimens (2); a summary of the trial design is presented in Table 1. Patients were randomly assigned to receive either monthly zoledronic acid or daily oral clodronate. Patients treated with zoledronic acid had a better chance of survival with an improvement in median OS of 5.5 months compared with patients treated with clodronic acid (ie, sodium clodronate) (hazard ratio [HR] of death = 0.84; 95% confidence interval [CI] = 0.74 to 0.96; P = .04). Notably, the survival benefit with zoledronic acid, observed within the first 6 months, remained statistically significant after adjustment for SREs (33), and thus it was consistent with clinically meaningful antimyeloma activity.

In multiple myeloma, the interaction between bone marrow stem cells and myeloma cells results in increased expression of receptor activator of nuclear factor kappa B ligand (RANKL) and decreased production of the osteoclast inhibitor, osteoprotegerin (OPG), favoring bone resorption (39). Denosumab, a human neutralizing antibody against RANKL that mimics the endogenous effect of OPG, has been tested in patients with myeloma (40). Denosumab has been investigated in two phase II studies of patients with myeloma who were previously treated with BPs, and both studies confirmed its efficacy in reducing SREs (41,42). In one of the trials using denosumab as a single agent to treat plateau phase or progressive myeloma, patients showed no substantial reduction in tumor burden, but some patients with progressive disease experienced disease stabilization (42). More recently, Henry et al. (43) reported the results of a phase III randomized trial that directly compared denosumab with zoledronic acid on skeletal morbidity and survival in patients with myeloma. Consistent with the other studies, denosumab was at least as effective as zoledronic acid in reducing the time to first SRE; however, in an unplanned analysis, the group treated with denosumab appeared to have a less favorable survival outcome (HR of death = 2.26, 95% CI = 1.13 to 4.50). Therefore, current findings indicate that both BPs and denosumab can effectively reduce SREs, but in multiple myeloma, denosumab may not have the antitumor activity of zoledronic acid.

Table 1. Summary of Medical Research Council Myeloma IX trial design*

Characteristic	Myeloma IX trial
Trial design	First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (Medical Research Council Myeloma IX): A randomized controlled trial (2).
Population	1,960 patients aged 18 years or older with newly diagnosed multiple myeloma.
Treatment	Patients were randomly assigned to receive 4-mg zoledronic acid iv every 3–4 week or 1600-mg sodium clodronate po daily.
Primary outcomes	Zoledronic acid reduced mortality by 16% (95% CI = 4% to 26%) compared with clodronic acid and extended median OS by 5.5 months (zoledronic acid vs clodronic acid, 50.0 months [IQR = 21.0 to not reached] vs 44.5 months [IQR = 16.5 to not reached]; *P* = .04). Zoledronic acid also statistically significantly improved PFS by 12% (95% CI = 2% to 20%) compared with clodronic acid and increased median PFS by 2.0 months, although this increase was not statistically significant (zoledronic acid vs clodronic acid, 19.5 months [IQR = 9.0 to 38.0 months] vs 17.5 months [IQR = 8.5 to 34.0 months]; *P* = .07).

* This large randomized trial was conducted to compare the bisphosphonates zoledronic acid and clodronic acid in patients newly diagnosed with myeloma receiving either intensive (high dose) or nonintensive standard dose chemotherapy. iv = intravenous; po = per os, ie, by mouth; CI = confidence interval; IQR = interquartile range, ie, 25th to 75th percentile; OS = overall survival; PFS = progression-free survival.

Anticancer Effects of Bisphosphonates in Breast Cancer

The earliest clinical studies used oral clodronate to test the potential efficacy of bone-targeted agents in preventing bone metastasis in early-stage (stages I–III) breast cancer (44–46). Although clodronate is a relatively weak bisphosphonate compared with the intravenous BPs that were developed subsequently (47), the effects of clodronate were sufficient to suggest that not only there was the potential to prevent bone metastases but that other effects on the disease course might be possible, thereby laying the groundwork for further clinical investigations. Subsequently, several large clinical trials have investigated the potential of adjuvant zoledronic acid to prevent recurrence of breast cancer (3,48,49).

Pilot and phase II studies in women with early-stage, high-risk breast cancer have reported that monthly zoledronic acid, in combination with standard anticancer therapy, can effectively increase DTC clearance and reduce DTC number and persistence in bone marrow compared with standard therapy alone (50–52). These zoledronic acid-mediated reductions in DTC persistence might be one of the mechanisms underlying the observed clinical benefits in studies such as the Austrian Breast and Colorectal Study Group (ABCSG)-12 trial (3), the ZOledronic acid and FemarA Synergy Trial (ZO-FAST) (48), and the Does Adjuvant Zoledronic acid redUce REcurrence in stage II/III breast cancer? (AZURE) trial (49); a summary of the trial designs is presented

in Table 2. However, bone marrow biopsies were not performed in these large clinical studies, and further studies are needed to determine whether benefits with zoledronic acid observed in disease-free survival (DFS) correlate with decreases in DTC levels.

In the ABCSG-12 trial, and with a median follow-up of 48 months (3), anticancer effects with zoledronic acid were seen both in bone and beyond; patients who received zoledronic acid in addition to standard endocrine therapy had fewer recurrences at all sites including visceral metastases and locoregional recurrence vs patients who did not receive zoledronic acid (control group) (3), results that were maintained at a median follow-up of 62 months (53). Moreover, after further follow-up (median = 84 months) of the whole study population, a persistent benefit in DFS events (locoregional recurrence, distant metastases, death without recurrence, or new primary cancer) more than 3 years after completion of treatment (HR of DFS event = 0.71, 95% CI = 0.55 to 0.92, *P* = .011) suggested a sustained, long-term "carryover" benefit from adding zoledronic acid to endocrine therapy (54). In addition (see Table 2), treatment with zoledronic acid also showed a statistically significantly improved OS compared with the control group (HR of death = 0.61, 95% CI = 0.39 to 0.96, *P* = .033) (54). Additionally, this most recent analysis suggested a statistically significant difference in zoledronic acid treatment effects on both DFS and OS based on patient age at enrollment. No statistically significant difference in DFS was observed between zoledronic acid-treated vs control groups of women aged 40 years or younger (HR of DFS event = 0.87, 95% CI = 0.55 to 1.36, *P* = .53), in whom suppression of ovarian function with goserelin may not be sufficient to fully suppress the production of estrogen and other reproductive hormones. However, among women older than 40 years of age at study entry, zoledronic acid showed a 34% reduction in the risk of DFS events compared with the control group of patients (HR of DFS event = 0.66; 95% CI = 0.48 to 0.92, *P* = .013) Zoledronic acid was also associated with a statistically significant 43% reduction in the risk of death from any cause (OS) in this older subset of patients (HR of death = 0.57; 95% CI = 0.33 to 0.99, *P* = .042) (54).

The Zometa–Femara Adjuvant Synergy Trials [European ZO-FAST (48), North American Z-FAST (55), and worldwide EZO-FAST (56)] were initiated primarily to investigate the bone-preserving activity of zoledronic acid during adjuvant therapy with aromatase inhibitors, and this suite of studies has provided important additional insights into the anticancer potential of zoledronic acid. In ZO-FAST, the preliminary results published previously (48) were confirmed at the final analysis after 60 months of follow-up (57); in addition to the bone mineral density benefits achieved with zoledronic acid, the immediate zoledronic acid group (treatment with zoledronic acid initiated at the start of adjuvant endocrine therapy) had a statistically significant 34% reduction in the risk of DFS events vs the delayed zoledronic acid (control) group (treatment with zoledronic acid initiated after bone fracture or decline in bone mineral density) (HR of DFS event = 0.66, 95% CI = 0.44 to 0.97, log-rank *P* = .038) (Table 2). Similar to the findings in ABCSG-12 trial, zoledronic acid initiation at the start of adjuvant endocrine therapy was associated with a reduction in breast cancer recurrence in and outside bone (57). Because patients in the control

Table 2. Summary of ABCSG-12, ZO-FAST, and AZURE trial designs*

Characteristic	Trial (reference)		
	ABCSG-12 (3,53,54)	**ZO-FAST (48,57)**	**AZURE (49)**
Population	1803 premenopausal women with endocrine-receptor-positive early-stage breast cancer receiving goserelin to induce menopause (3.6 mg every 28 days).	1065 postmenopausal women with early-stage breast cancer receiving letrozole (2.5 mg per day for 5 years).	3360 pre and postmenopausal women with early-stage breast cancer receiving standard chemotherapy and/or hormonal therapy.
Treatment	Patients were randomly assigned to receive anastrozole (1 mg per day) or tamoxifen (20 mg per day) with or without zoledronic acid (4 mg every 6 months) for 3 years.	Patients were randomly assigned to receive immediate zoledronic acid (4 mg every 6 months) or delayed zoledronic acid (initiated only for fracture or high risk thereof).	Patients were randomly assigned to receive zoledronic acid 4 mg every 4 weeks ×6, then every 3 months ×8, then every 6 months until 5 years or until first evidence of distant metastases.
Primary outcomes	Zoledronic acid group had a 29% relative risk reduction for DFS (HR DFS event = 0.71, 95% CI = 0.55 to 0.92; P = .011) (54). Benefit largely restricted to women aged >40 years at study entry.	Immediate zoledronic acid group had a 34% relative risk reduction for DFS (HR of DFS event = 0.66, 95% CI = 0.44 to 0.97; P = .038) (57).	No differences in DFS or OS in ITT population. In patients who were postmenopausal for at least 5 years before study entry, zoledronic acid group had a 25% relative risk reduction for invasive DFS (HR of DFS event = 0.75, 95% CI = 0.59 to 0.96; P = .02) and the risk of death by 26% (HR of death = 0.74, 95% CI = 0.55 to 0.98 P = .04).

* Summary of populations, treatment schedules, and primary outcomes in key trials evaluating the adjuvant use of bone-targeted agent zoledronic acid in early-stage (stages I–III) breast cancer. All P values quoted are two-sided. ABCSG-12 =Austrian Breast and Colorectal Study Group-12; ZO-FAST = ZOledronic acid and FemarA Synergy Trial; AZURE = Does Adjuvant Zoledronic acid redUce REcurrence in stage II/III breast cancer?; HR = hazard ratio; CI = confidence intervals; DFS = disease-free survival; OS = overall survival; ITT = intention to treat.

arm of ZO-FAST experiencing either a fragility fracture or a pro-tocol-defined decline in bone mineral density received delayed intervention with zoledronic acid, an analysis censoring patients in the delayed arm at commencement of delayed zoledronic acid was performed. This showed a slightly larger benefit from immediate zoledronic acid on DFS (HR of DFS event = 0.62, 95% CI = 0.41 to 0.93, P = .024) (57).

In the AZURE trial, although treatment with zoledronic acid did not show a statistically significantly increase in DFS compared with standard therapy alone in the overall (intention to treat) population (HR of DFS event = 0.98, 95% CI = 0.85 to 1.13, P = .79), prospective analyses based on the menopausal status of the patients at study entry revealed treatment benefit in some patients (Table 2) (49). Among pre or perimenopausal patients, there was no appreciable difference between zoledronic acid and standard therapy groups for DFS (HR of DFS event = 1.15, 95% CI = 0.97 to 1.36, P = .11) or OS (HR for death = 0.97, 95% CI = 0.78 to 1.21, P = .81). In contrast, among patients who were postmenopausal for at least 5 years before study entry, treatment with zoledronic acid showed a statistically significantly reduced risk of DFS events by 25% (HR of DFS event = 0.75, 95% CI = 0.59 to 0.96, log-rank P = .02) (Table 2) and the risk of death from any cause (OS) by 26% (HR for death = 0.74, 95% CI = 0.55 to 0.98, log-rank P = .04) (49). Although this subset constituted only a relatively small proportion of the AZURE trial population (~30%), in the general population of patients with breast cancer the majority of patients (~70%) are in this older demographic subset for whom use of adjuvant zole-dronic acid might be expected to echo the findings observed in the postmenopausal population of the AZURE trial. Most interestingly,

although the effect of zoledronic acid on distant skeletal recurrence was similar in the different menopausal status groups (heterogeneity test χ^2_1 = 0.14, P = .70), for the other components of invasive DFS (extraskeletal distant recurrence, locoregional recurrence, second malignancy) there was a statistically significant difference in treatment effect according to menopausal status, with an apparent benefit in women more than 5 years postmenopause and potential harm in all other women (premenopausal, perimenopausal within 5 years of last menses, and menopausal status unknown; heterogeneity test χ^2_1 = 14.00, P < .001) (49). Although the underlying mechanisms for this benefit in an estrogen-depleted patient subset have yet to be entirely elucidated, they are consistent with the profound DFS benefits detected in the exploratory analyses of the older patient (age > 40 years) subset of the ABCSG-12 trial (54).

Data with other bone-targeted agents are limited, but preliminary results from randomized trials evaluating oral clodronate (National Surgical Adjuvant Breast and Colorectal [NSABP]-B34 study; ClinicalTrials.gov Identifier NCT00009945) (58) and oral ibandronate (German adjuvant ibandronate study [GAIN]; ClinicalTrials.gov Identifier NCT00196872) (59) have recently been presented. In NSABP-B34, with a median follow-up of 8.4 years, oral clodronate had no statistically significant effect on DFS or OS in the total study population. However, similar to the findings in AZURE, a statistically significant reduction in distant metastasis was seen in patients over the age of 50 years (a surrogate for postmenopausal status) treated with clodronate (HR of distant DFS event = 0.62, 95% CI = not stated, P = .003) (58). Again the benefit was greatest in preventing recurrence at extraskeletal sites. In the GAIN trial, median follow-up was short

(31 months), and no statistically significant differences in DFS (HR of DFS event = 0.94, 95% CI = 0.77 to 1.02, P = .59) or OS (HR for death = 1.04, 95% CI = 0.763 to 1.42, P = .80) between the ibandronate and placebo treated groups were seen. There was a trend in favor of ibandronate in postmenopausal women or those over the age of 60 years, but insufficient events have occurred for reliable subgroup analyses (59).

The results from NSABP-B34 (58) and the previous clodronate study by Powles et al. (46) suggest that contrary to the observations in preclinical studies and in the clinical setting of multiple myeloma, the beneficial effects of BPs in solid tumors may be less dependent on the type of agent chosen and more on the hormonal status of the patient. The ongoing South West Oncology Group (SWOG) clinical trial SWOG-0307 (ClinicalTrials.gov Identifier NCT00127205) (60) comparing zoledronic acid, ibandronate, and clodronate has recently completed accrual and will address the relative efficacy of different BPs. There are also ongoing adjuvant studies with denosumab; ABCSG-18 (ClinicalTrials.gov Identifier NCT00556374) (61) is a placebo controlled study of monthly administration of denosumab 60 mg for 6 months in postmenopausal women receiving an aromatase inhibitor, whereas the D-CARE study (ClinicalTrials.gov Identifier NCT01077154) (62) is evaluating a more intensive schedule of denosumab 120 mg, administered initially monthly for 6 months and then every 3 months thereafter in stage II–III breast cancer.

The apparent treatment interaction between reproductive hormone levels and BP effects is being investigated by several groups but is unlikely to be mediated by estradiol alone. At menopause, serum estradiol declines over several years to low levels, follicle stimulating hormone (FSH) levels rise, and inhibin (a protein known to inhibit FSH biosynthesis) falls to undetectable levels (63). In the absence of inhibin, the TGF-β ligand, activin (known to activate FSH biosynthesis) becomes the dominant signaling molecule in bone, binding to the activin type II receptor and resulting in phosphorylation and activation of the SMAD family of proteins known to have important effects on both bone and cancer cell functions. The endocrine changes across the menopausal transition have been extensively reviewed by Nicks et al. (63).

Anticancer Effects in Solid Tumors

In advanced cancer, the evidence that bone-targeted agents may beneficially affect survival emerged from the secondary endpoints of the phase III registration studies of zoledronic acid in patients with metastatic bone disease. In patients with bone metastases from hormone-refractory prostate cancer (HRPC; n = 422 patients) or renal cell carcinoma (RCC; n = 46 patients), trends toward improved OS in patients treated with zoledronic acid were seen (64).

Approximately two-thirds of more than 1400 patients with known metastatic bone disease entering into the phase III trials of zoledronic acid had baseline urinary n-telopeptide of type 1 collagen (NTX) levels at or above the normal threshold for young healthy adults (50 nmol/mmol creatinine) (65). This increase in bone resorption correlated with more rapid rates of skeletal morbidity, shorter time to disease progression, and increased risk of death (66).

Treatment with zoledronic acid results in normalization of elevated NTX levels in the majority of patients with bone metastases from solid tumors (67), and this may have indirect effects on the disease course. A retrospective analysis of the zoledronic acid phase III trial database demonstrated that in patients with elevated baseline NTX levels, NTX normalization within 3 months of initiating zoledronic acid correlated with improved OS compared with patients who had persistently elevated NTX (67). Furthermore, in a subsequent meta-analysis of placebo-controlled trials in patients with a wide range of solid tumors and elevated baseline NTX levels (≥100 nmol/mmol creatinine), zoledronic acid treatment reduced the risk of death by 26% compared with the placebo group (P = .006) (68). This survival advantage with zoledronic acid was maintained when SRE incidence as a competing time-dependent variable was included. Consistent with this meta-analysis, statistically significant survival benefits were seen in metastatic non-small cell lung cancer (NSCLC) patients with elevated baseline NTX. Here, zoledronic acid reduced the risk of death by 35% compared with placebo (P = .024) (69).

Factors contributing to these possible survival benefits in advanced malignancy include the prevention of fractures. Pathologic fractures increase the risk of death in both HRPC and breast cancer (70). In patients with bone metastases from HRPC, zoledronic acid reduced the incidence of pathologic fractures by 32% and prolonged the time to first pathologic fracture by 6.5 months compared with placebo (both P = .02) (71). Zoledronic acid could therefore indirectly prolong survival in patients with bone metastases through 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. Of note, the survival impact is greatest in those patients with NSCLC, whose survival is typically short and for whom a delay in anticancer treatment of a few weeks may have more bearing on subsequent outcome (69).

Two placebo-controlled trials of oral clodronate have recently reported 10-year survival rates in men with prostate cancer with (n = 311 patients) or without metastatic disease (n = 508 patients) (72). Clodronate was associated with an OS benefit among men with metastatic disease compared with placebo (HR for death = 0.77, 95% CI = 0.60 to 0.98, P = .032) (72). However, among men without metastatic disease, there was no evidence of an OS benefit with clodronate compared with placebo (HR for death = 1.12; 95% CI = 0.89 to 1.42, P = .94) (72).

A recent phase III study has evaluated the ability of denosumab to prevent bone metastasis or death from any cause in men with nonmetastatic castration-resistant prostate cancer (CRPC). A total of 1432 men with nonmetastatic CRPC at high risk for bone metastasis (prostate-specific antigen [PSA] ≥ 8.0 ng/mL and/or PSA doubling time ≤ 10.0 months) were randomized to receive monthly subcutaneous denosumab 120 mg or placebo (4). The primary endpoint was bone metastasis-free survival (BMFS), a composite endpoint determined by time to first occurrence of bone metastasis (symptomatic or asymptomatic) or death. Denosumab statistically significantly increased BMFS by a median of 4.2 months compared with placebo (HR for BMFS = 0.85, 95% CI = 0.73 to 0.98, P = .028). Denosumab also statistically significantly delayed time to first bone metastasis (HR of bone metastasis = 0.84, 95% CI = 0.71 to 0.98, P = .032). However, OS was similar between groups (HR for death = 1.01, 95% CI = 0.85 to 1.20, P = .91) (4).

Table 3. Magnitude of benefit with adjuvant treatments in early-stage (stages I–III) breast cancer*

Adjuvant treatment		Absolute difference in DFS at 5 years, %	HR (95% CI)	P†	Reference
CMF vs no CMF		NR	0.76 (NR)	<.001	(77)
Adjuvant anthracycline vs CMF		6	0.69 (0.58 to 0.82)	<.001	(78)
Docetaxel (TAC) vs FAC		7	0.72 (0.59 to 0.88)	.001	(79)
Tamoxifen vs no tamoxifen		14.2‡	0.61 (0.57 to 0.65)	<.001	(80)
Anastrazole	Tamoxifen	2.4	0.87 (0.78 to 0.97)	.01	(81)
Letrozole	Tamoxifen	1.9	0.81 (0.70 to 0.93)	.003	(82)
Trastuzumab	No trastuzumab	6.4	0.76 (0.66 to 0.87)	<.001	(83)
Zoledronic acid	No zoledronic acid	4.5	0.71 (0.55 to 0.92)	.011	(54)

* Table illustrates the absolute benefit obtained with the use of zoledronic acid compared with other widely used and approved adjuvant treatments for early-stage (stages I–III) breast cancer at a median follow-up of 5 years, except in one study. DFS = disease-free survival; HR = hazard ratio; CI = confidence interval; CMF = cyclophosphamide, methotrexate, and fluorouracil; NR = not reported; TAC = docetaxel, adriamycin, and cyclophosphamide; FAC = fluorouracil, adriamycin, and cyclophosphamide.

† P values were calculated using two-sided log-rank test.

‡ Reduction in DFS at a median follow-up of 10 years.

Zoledronic acid has also demonstrated progression-free and OS benefits in some small pilot studies in patients with and without bone metastases (73,74). Additionally, patients with bone metastases from lung cancer (n = 144 patients) receiving standard chemotherapy and zoledronic acid (4 mg iv administration every 21–28 days for 1 year) for bone pain had longer median survival (51% improvement) compared with patients receiving standard chemotherapy but not receiving zoledronic acid (578 vs 384 days, respectively; P < .001) (75).

Ongoing trials are evaluating the efficacy of zoledronic acid for improving clinical outcomes, such as survival, in more than 7 000 men with stage III and castrate sensitive metastatic prostate cancer receiving androgen-deprivation therapy. Potential anticancer effects of zoledronic acid are also being assessed in patients with lung cancer (Study 2419; ClinicalTrials.gov Identifier NCT00172042) (76). Results from these studies, along with the large breast cancer adjuvant program with a variety of bone-targeted agents, will help define the clinical importance of the anticancer effects of bone-targeted therapies.

Conclusions

There is a growing body of evidence demonstrating the anticancer benefits with bone-targeted treatments, notably with zoledronic acid. Both menopausal women with early-stage (stages I, II, and III) breast cancer and patients with myeloma experience survival benefits that are of a similar magnitude to those observed with currently accepted anticancer approaches (54,77–83) (Table 3). In the early-disease setting, for large subgroups of patients including men with hormone refractory prostate cancer and women with breast cancer in the absence of circulating reproductive hormones, there is increasing evidence that changing the bone marrow environment appears to prevent metastatic disease at sites other than bone. The durability of the response is important, with a carryover effect demonstrated in some tumor types at greater than 6 years follow-up.

A number of mechanisms to describe the anticancer effects observed have been identified, but it is not clear yet whether there is an integrating hypothesis that bridges all tumor types. In each tumor subtype, it may be that different combinations of mechanisms interact to create the effect.

Many questions still remain. What is the role of other bone targeting agents, what is the optimum treatment intensity, and how long should treatment be administered? Studies are ongoing, which will answer some of these questions. Clearly the risks associated with zoledronic acid are small in the context of the benefits gained and the costs of treatment, particularly when administered at a frequency less than every 3–4 weeks, are low.

In myeloma, the evidence suggests that we should be offering zoledronic acid to all patients at diagnosis, irrespective of the presence of bone disease. Treatment should probably be continued for in excess of 2 years, but it may be that after treatment for 2 years, or in patients in complete remission, that dosing intensity can be reduced.

The case has already clearly been made as to the benefits of zoledronic acid in advanced breast cancer. In early disease, zoledronic acid should be offered to all patients who, as a result of either age or medically induced ovarian suppression, have a lack of circulating estrogen.

In other solid tumors, bone-targeted agents should be considered in the routine care of patients with metastatic bone disease. For those with rapid bone destruction, survival benefits may be seen, although data are emerging to suggest that delay in development of bone metastasis is possible.

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