Adjuvant Bisphosphonate Therapy in Postmenopausal Breast Cancer Patients

Michael Gnant

Universitätsklinik für Chirurgie, Medizinische Universität Wien, Austria

Key Words

Breast cancer · Bone loss · Bisphosphonates · Adjuvant therapy

Summary

Adjuvant bisphosphonate therapy is increasingly used in postmenopausal breast cancer patients. This is based on level-one evidence that bisphosphonates, particularly zoledronic acid, can effectively prevent cancer treatment-induced bone loss in breast cancer patients receiving estradiol-lowering endocrine therapies such as aromatase inhibitors. Furthermore, emerging data from large clinical trials suggest that additional anti-cancer benefits can be derived due to a positive impact on the bone marrow microenvironment.

Schlüsselwörter

Brustkrebs · Knochendichteverlust · Bisphosphonate · Adjuvante Therapie

Zusammenfassung

Adjuvante Bisphosphonattherapie wird bei postmenopausalen Brustkrebspatientinnen vermehrt zur Anwendung gebracht, basierend auf Level-1-Evidenz, dass Bisphosphonate, insbesondere Zoledronat, den therapieinduzierten Knochendichteverlust effektiv verhindern können. Knochendichteverlust ist eine häufige Folge von endokrinen Standardtherapien, die den Östrogenspiegel senken, wie z.B. Aromataseinhibitoren. Zusätzlich zeigen Daten aus großen klinischen Studien, dass darüber hinaus eine antitumorale Wirksamkeit besteht, basierend auf günstiger Beeinflussung des molekularen Klimas im Knochenmark.

Introduction

Breast cancer is the leading cause of cancer-related deaths among women worldwide [1]. Advances in treatment for breast cancer have substantially improved survival and clinical outcomes in recent years [2]. For endocrine-responsive breast cancer, endocrine therapy has become the standard adjuvant treatment after locoregional treatment. Endocrine therapies for breast cancer profoundly decrease circulating estrogen levels. This can be associated with marked decreases in bone mineral density (BMD) in some patients. Aromatase inhibitors (AIs) are nowadays the endocrine therapy of choice in postmenopausal women with endocrine-responsive breast cancer [3]. By inhibition of the enzyme aromatase, these agents suppress estrogen production in peripheral tissues and

reduce estrogens to below normal postmenopausal levels. This can lead to significant impact on bone health in addition to the physiological menopausal risk of osteoporosis [4]. Outside a breast cancer setting, the annual bone loss in postmenopausal women is approximately 1% versus 0.4% or less in premenopausal women [5]. In addition to this background risk, AI therapy for breast cancer is associated with accelerated bone loss (approximately 2.6% BMD loss annually) compared with healthy untreated postmenopausal women [6]. It is believed that cancer therapy-induced bone loss (CTIBL) occurs more rapidly and in many patients is of greater magnitude compared with postmenopausal osteoporosis. Pharmacologic intervention may be indicated to prevent such treatment-induced side effect, ban the risk of subsequent fractures, and thus preserve patients' quality of life (QOL).

Available Options to Prevent Treatment-Induced Bone Loss during Endocrine Therapy for Breast Cancer

Physiologic remodeling of bone is characterized by a balance between resorption of existing bone by osteoclasts and formation of new bone by osteoblasts [7]. Estrogen as well as other local and systemic factors regulate these processes. Receptor activator of nuclear factor kappa B (RANK) is a cell surface receptor expressed by immature and mature osteoclasts and is important for osteoclast maturation and activation. Binding of RANK to its ligand (RANK-L which is produced locally by osteoblasts and other stromal cells in response to systemic signals) is necessary for osteoclast fusion, differentiation, and maturation. During estrogen-lowering breast cancer treatment, osteoclast-mediated osteolysis is increased, resulting in overall bone loss. Prevention of this unwanted side effect requires so-called antiresorptive agents, e.g. bisphosphonates (BPs) or RANK-L inhibitors.

Bisphosphonates

BPs are antiresorptive agents that induce osteoclast apoptosis. They are divided into 2 categories based on their chemical structure [8]. Early-generation non-nitrogen-containing BPs (e.g. clodronate and etidronate) are small-molecule pyrophosphate analogues that bind to the bone surface via their carbon-phosphate P-C-P backbone. These agents are internalized by osteoclasts during bone resorption, resulting in the accumulation of cytotoxic levels of BP metabolites in osteoclasts. Nitrogen-containing BPs (N-BPs; e.g. pamidronate, ibandronate, risedronate, and zoledronic acid (ZOL)) also accumulate in bone and are preferentially taken up by osteoclasts. In contrast to early-generation non-nitrogen-containing BPs, however, they also inhibit the mevalonate pathway of posttranslational protein modification.

The currently approved use of BPs is for the treatment of menopausal osteoporosis and for patients with bone metastases. In the latter group, intravenous N-BPs have proven efficacy for preventing skeletal-related events (SREs). By reducing the frequency of hypercalcemia, pathologic fractures, as well as the need for palliative radiation or surgery to bone, these drugs improve QOL in patients with bone metastases from breast cancer, also by palliating bone pain.

RANKL Inhibitors

Osteoclast maturation and activation is dependent on the RANK/RANK-L pathway. Under physiologic conditions, RANK-L function is regulated by its soluble competitive (decoy) receptor, osteoprotegerin (OPG). Changes in the RANK-L:OPG ratio by any cause result in unbalanced bone turnover which is also what happens during endocrine treatment of breast cancer. Inhibitors of RANK-L therefore decrease bone resorption and prevent bone loss. Denosumab is a monoclonal antibody that inhibits RANK-L and suppresses bone resorption marker levels in patients with bone metas-

tases from solid tumors. Several trials are ongoing to evaluate the efficacy of denosumab in the early and metastatic cancer settings, and an early report of a small study indicates that denosumab can also prevent CTIBL in the adjuvant setting of breast cancer patients [8].

Adjuvant Trials Using Bone-Targeted Therapies to Prevent or Treat CTIBL

A small trial of clodronate in postmenopausal women receiving oral antiestrogen therapy (tamoxifen or toremifene) for 3 years demonstrated limited efficacy in the prevention of cancer therapy-associated bone loss [9]. In this study, postmenopausal women ($n = 61$) with operable breast cancer were randomized to antiestrogen therapy plus placebo or clodronate (1,600 mg orally once daily) for 3 years. After 3 years, lumbar spine BMD deteriorated in patients receiving antiestrogen therapy alone but improved in clodronate-treated patients (+1.0% vs. -1.7% for no clodronate; $p = 0.01$). At the 5-year follow-up (2 years after completion of clodronate therapy), although patients in both groups experienced BMD loss, lumbar spine BMD remained higher versus baseline in patients who had received clodronate (-1.0% vs. -3.2% for no clodronate; $p = 0.06$).

Risedronate has also been evaluated for prevention of bone loss in the postmenopausal breast cancer setting. In a study of risedronate in postmenopausal women receiving the AI anastrozole ($n = 118$), bone loss in the total study population was significant compared with age-matched controls (mean BMD change, -3.3%; $p < 0.0001$) [10]. In the osteoporotic cohort in this study ($n = 15$), risedronate prevented further bone loss at the hip and improved BMD at the spine (+ 4.1% vs. baseline; $p = 0.008$). In a separate study of risedronate in postmenopausal patients who had undergone chemotherapy for breast cancer ($n = 87$), patients were randomized to placebo or weekly risedronate (35 mg orally) for 2 years, with concomitant endocrine therapy if required. Approximately 70% of patients received tamoxifen, toremifene, or fulvestrant during the course of the study. At the end of 2 years, BMD measurements at the spine and hip were 1.6–2.5% lower in the placebo arm compared with the risedronate arm ($p < 0.05$). In this study, patients receiving placebo and no AI had stable BMD at the spine and a small decrease in BMD at the hip. In contrast, women receiving placebo plus AI experienced a mean BMD decrease of 4.8% at the spine and 2.8% at the hip ($p < 0.001$ vs. baseline for both). Risedronate partially protected BMD in all subgroups. Lumbar spine BMD decreased by 2.4% in the risedronate plus AI arm; hip BMD remained stable in the risedronate plus AI arm and improved by 2.2% in the risedronate and no AI arm. Some of these results are promising, but there is only a limited number of patients in these studies, and compliance issues may limit the applicability of oral BPs to larger patient

cohorts. Currently, several trials have been planned or started to further evaluate oral BPs such as risedronate and ibandronate for prevention of CTIBL:

The N02C1 study randomized 220 women undergoing adjuvant or neoadjuvant chemotherapy for stage I–IIIb breast cancer to placebo or weekly oral risedronate. After 1 year, change in BMD (lumbar spine, hip, and femoral neck) was similar between the 2 treatment groups ($p > 0.1$ for risedronate vs. placebo at all sites), showing that risedronate (35 mg orally weekly) does not prevent CTIBL [11, 12]. In another ongoing study (SABRE), patients undergoing AI (anastrozole) therapy for breast cancer with baseline BMD less than -1.0 at either the hip or the spine but at least -2.0 at both sites were randomized to risedronate (35 mg orally weekly; $n = 73$) or placebo ($n = 65$). At the 12-month follow-up, BMD was significantly increased in patients receiving anastrozole and risedronate versus anastrozole alone: $+1.71\%$ at the lumbar spine (vs. -0.41% ; $p < 0.0001$) and $+1.29\%$ at the hip (vs. -0.09% ; $p = 0.002$). Levels of biochemical markers of bone turnover reflected the observed BMD changes, indicating that risedronate treatment suppresses elevated bone metabolism in women receiving AI therapy for breast cancer [13]. A third study of risedronate in women undergoing AI therapy for breast cancer (IBIS-II) enrolled 613 women in the bone substudy [14]. In women with normal baseline BMD ($n = 162$), anastrozole treatment for 12 months significantly decreased BMD compared with placebo at the lumbar spine (-2.5% vs. -0.97% ; $p = 0.002$) and hip (-1.34% vs. -0.37% ; $p = 0.02$); risedronate was not investigated in this cohort. In women who were osteopenic at baseline, concomitant risedronate significantly decreased anastrozole-associated bone loss at the hip compared with anastrozole alone ($+0.67\%$ vs. -2.27% , respectively; $p = 0.01$). Similar changes were observed in lumbar spine BMD, but the differences did not attain statistical significance. Thus, concomitant treatment with risedronate prevents AI-associated bone loss in women with baseline osteopenia. The efficacy of risedronate for prevention of AI-associated bone loss in women with normal baseline BMD is yet to be determined.

The ARIBON trial is evaluating the efficacy of ibandronate (150 mg orally every month) for the prevention of AI-associated bone loss in postmenopausal women receiving adjuvant anastrozole therapy for hormone-responsive breast cancer [15]. In this study, women with baseline osteopenia ($n = 50$) were randomized to anastrozole with either placebo or monthly ibandronate. At the 12- and 24-month follow-up, BMD was decreased compared with baseline in the placebo arm, whereas BMD was substantially increased in the ibandronate arm. Changes in lumbar spine BMD at 12 and 24 months were $+3.11\%$ and $+2.98\%$, respectively, in patients receiving ibandronate concomitant with anastrozole versus -2.35% and -3.22% , respectively, in those receiving anastrozole with placebo ($p < 0.01$ at each time point). Ibandronate also effectively reduced bone turnover marker levels at

12 months, indicating that ibandronate suppresses elevated bone metabolism in patients undergoing AI therapy.

The largest trials of BPs for the prevention of bone loss in the postmenopausal breast cancer setting involve zoledronic acid (ZOL). The Z-FAST, ZO-FAST and E-ZO-FAST trials are 3 parallel companion trials evaluating the efficacy of ZOL (4 mg intravenously (IV) every 6 months) for prevention of AIBL in postmenopausal women receiving adjuvant endocrine therapy for hormone-responsive, stage I–IIIa breast cancer [16]. In these trials, patients with a baseline BMD T-score of more than -2.0 (normal or osteopenic) were randomized to letrozole (2.5 mg orally once daily) and either upfront ZOL (initiated ≤ 14 days after start of letrozole therapy) or delayed ZOL (initiated in patients with post-baseline BMD T-score < -2.0 or non-traumatic fracture). Integrated analysis of the Z- and ZO-FAST studies (total $n = 1,667$) demonstrated significant differences in the percentage change in lumbar spine (5.2% ; $p < 0.0001$) and total hip (3.5% ; $p < 0.0001$) BMD between the upfront and delayed groups at the 12-month follow-up. At the 24-month follow-up, fracture rates were similar between the 2 arms; however, a substantial proportion of fractures in the upfront-ZOL arm occurred in osteopenic women, whereas fractures were more common among women with normal BMD in the delayed-ZOL arm. Similar differences were observed at the 12-month follow-up in the E-ZO-FAST trial ($n = 522$): patients in the upfront-ZOL arm had a mean lumbar spine BMD increase of 2.7% compared with baseline versus a mean decrease of 2.7% in the delayed-ZOL arm ($p < 0.0001$) [17]. Total hip BMD was also significantly improved in the upfront-ZOL group compared with substantial deterioration in the delayed-ZOL group (again, $p < 0.0001$ for between-group difference). Thus, the Z/ZO/E-ZO-FAST trials demonstrate prevention of AIBL and consistently improved BMD with twice-yearly ZOL treatment in more than 2,000 women with early breast cancer.

A large trial (CALGB 79809) is ongoing to evaluate the efficacy of ZOL (4 mg every 3 months) for prevention of bone loss in women with early stage breast cancer, who were premenopausal at baseline but who developed chemotherapy-induced ovarian failure [18]. In this study, women with stage I–III breast cancer were randomized to adjuvant chemotherapy (with or without tamoxifen) and ZOL (4 mg IV every 3 months initiated with chemotherapy; upfront ZOL) or after 12 months of chemotherapy alone (late ZOL). In the subset of patients who developed ovarian failure ($n = 166$), change in lumbar spine BMD from baseline at 12 months was -6.6% in patients receiving chemotherapy alone versus $+2.2\%$ in patients receiving chemotherapy with upfront ZOL ($p < 0.0001$). No results have been reported to date for the late ZOL cohort. Addition of tamoxifen to chemotherapy decreased but did not prevent bone loss (BMD change: -4.3% for chemotherapy plus tamoxifen vs. -9.5% for chemotherapy alone). Concomitant treatment with ZOL was equally effective in

both groups. Future analyses from this trial (including data from the late-ZOL group) will address the optimal timing of ZOL in premenopausal patients undergoing adjuvant chemotherapy for breast cancer.

The fully humanized monoclonal antibody against RANK-L, denosumab, is also being evaluated for prevention of AI-associated bone loss. The HALT-BC trial is a phase III, double-blind study in which 252 patients with breast cancer and low baseline BMD (T-score ≤ -1.0 but ≥ -2.5) undergoing adjuvant AI therapy for breast cancer were randomized to placebo (n = 125) or denosumab (60 mg subcutaneously every 6 months; n = 127) for 2 years [9]. In the placebo arm, lumbar spine BMD decreased substantially during 2 years of AI therapy. Denosumab prevented AIBL and substantially improved BMD compared with baseline. Between-group differences in lumbar spine BMD were 5.5% at 12 months and 7.6% at 24 months ($p < 0.0001$ for both). Similar improvements in BMD were observed at the hip, femoral neck, and trochanter. These results with denosumab appear promising and warrant further investigation into the safety and efficacy in larger patient populations. A second, larger ongoing trial of denosumab in postmenopausal women undergoing AI therapy for breast cancer (ABCSG-18) has an updated target accrual of approximately 3,200 women [19].

Prevention of Recurrence in Breast Cancer – Anticancer Effect of Antiresorptive Agents

A large body of preclinical evidence shows that N-BPs possess inherent anticancer activity. Both in vitro and in vivo studies have demonstrated antiproliferative and proapoptotic efficacy of BPs, alone as well as synergistically with cytotoxic agents (reviewed in Mundy, 2002 [20] and Winter et al., 2008 [21]). Their antitumor function is due to several mechanisms namely i) inhibition of tumor cell proliferation, ii) inhibition of tumor cell adhesion, iii) synergy with cytotoxic products, and iv) indirect effects like inhibition of angiogenesis or stimulation of immune surveillance [9, 22]. In addition, therapeutic approaches aiming at changing the microenvironment in which dormant tumor cells survive, may be of particular importance in early disease where these dormant tumor cells are the source of late relapse and disease progression [23]. It has been proposed that tumor stem cells may play a major role in the generation of these quiescent dormant tumor cells which may reside in the ‘vascular niche’ of the bone marrow [24].

Several BPs inhibit tumor cell migration and invasion in preclinical models. In addition, ZOL has demonstrated anti-angiogenic properties and activates the immune system against cancer cells, which might contribute to its overall antitumor actions. The molecular mode of action of ZOL is its impact on the mevalonate pathway. By inhibition of the enzyme metabolizing farnesyl diphosphate (FPP), accumulation of FPP will occur, which has been shown to attract immune

cells in a variety of settings. In addition, ZOL appears to have an inhibitory effect on pathways further downstream via inhibition of the prenylation of small G-proteins such as Ras, Rap1, Rho, and Rab8a, which are necessary for tumor cell proliferation and other important tumor cell functions.

Overall, the combined preclinical and early clinical data suggest that the addition of BPs to conventional cancer therapy may provide tangible antitumor and antimetastatic benefits for patients with primary cancers that have a high frequency of metastasis to bone [25]. As a result, numerous studies are investigating the antitumor potential of BPs in the breast cancer setting. The potential antimetastatic efficacy of clodronate has been evaluated in 3 clinical trials. In an elegant study of patients with stage I–III breast cancer (n = 1,069) and selected for tumor cell positivity in their bone marrow were randomized to standard adjuvant therapy alone or with concomitant daily clodronate (1,600 mg orally for 2 years). Oral clodronate significantly reduced the risk of bone metastases in the overall study population (hazard ratio (HR) = 0.692; $p = 0.043$) at a median follow-up of 5.6 years. Benefits were more pronounced for patients with stage II/III breast cancer (HR = 0.592; $p = 0.009$). Overall survival (OS) was also improved by approximately 23% ($p = 0.048$) in the clodronate arm [26, 27]. Clodronate was also found to reduce the risk of distant metastases in patients with breast cancer and tumor cells in bone marrow. Patients (n = 302) were randomized to standard adjuvant therapy alone (n = 145, control arm) or with daily clodronate (1,600 mg orally for 2 years; n = 157). After 36 months follow-up, the number of patients with distant metastases was significantly smaller in the clodronate arm compared with controls (21 vs. 42; $p < 0.001$). Incidence of skeletal or visceral metastases was significantly lower in the clodronate arm ($p = 0.003$ for both), and fewer patients receiving clodronate died during this 36-month period (6 vs. 22 in the control group; $p = 0.001$). Long-term follow-up of this trial revealed that OS at 8.5 years was 79.6% in the clodronate group versus 59.3% in the control group ($p = 0.049$). However, a third trial of clodronate in women with primary node-positive breast cancer yielded conflicting results [28]. This study randomized patients (n = 299) to adjuvant therapy alone (control arm, n = 150) or with daily clodronate (1,600 mg orally for 3 years; n = 149) and initially followed the patients for 5 years. The incidence of bone metastases was similar in the clodronate and control arms (21% vs. 17%; $p = 0.27$); however, 43% of patients in the clodronate arm developed visceral metastases compared with 25% in the control arm ($p = 0.0007$), resulting in significantly lower rates of disease-free survival (DFS; 56% vs. 71%; $p = 0.007$) and OS (70% vs. 83%; $p = 0.009$) in the clodronate group. A 10-year follow-up of this trial confirmed significantly higher rates of non-skeletal metastases (visceral or local) in the clodronate arm compared with control (50% vs. 36%; $p = 0.005$). At 10 years, DFS remained lower in the clodronate arm, particularly for patients with hormone receptor-negative

disease (25% for clodronate vs. 58% for control; $p = 0.004$), but OS rates were similar between groups. Overall, clodronate trials in the adjuvant setting provide promising but inconclusive results. A meta-analysis of these studies revealed no significant benefit of clodronate treatment in patients with early breast cancer (OS HR = 0.75; 95% confidence interval 0.31–1.82) [29].

As discussed in preceding sections, the benefits of adding BPs to standard adjuvant therapy for maintaining skeletal health are now well established through several studies. Recent trials using more active BPs in the adjuvant setting in breast cancer are providing better insight into the potential for benefits from BPs that may extend beyond skeletal health. In fact, ZOL has demonstrated promising antitumor activity in several small pilot trials. In a recent study, patients with bone metastases from bladder cancer ($n = 40$) were randomized to placebo or ZOL (4 mg IV every 28 days) for 6 months [30]. After a median follow-up of 183 days, ZOL significantly reduced the incidence of SREs and bone pain compared with placebo ($p \leq 0.015$ for both). In addition, ZOL significantly improved the 1-year survival rate compared with placebo (30% vs. 5%; $p = 0.02$). ZOL (4 mg IV every 28 days) has also demonstrated anticancer efficacy in patients undergoing chemotherapy for previously untreated multiple myeloma ($n = 94$) [31]. At a median follow-up of 49.6 months, 5-year OS estimates improved from 46% in the chemotherapy-alone arm to 80% in the chemotherapy-plus-ZOL arm ($p < 0.01$). In addition, ZOL reduced the incidence of SREs. Thus, addition of ZOL to conventional chemotherapy not only reduced skeletal morbidity in patients with multiple myeloma but also improved survival. In a third pilot study, patients with advanced solid tumors and no evidence of bone metastases ($n = 40$) were randomized to monthly ZOL or no treatment (control) and followed until bone metastases were detected [32]. After the 12-month follow-up, bone metastases-free survival was 60% in the ZOL arm versus 10% in the control arm ($p < 0.0005$). This difference was still detectable at the 18-month follow-up, at which time 20% of patients in the ZOL group were free of bone metastases compared with only 5% in the control group ($p = 0.0002$).

Emerging data also indicate that ZOL effectively reduces the prevalence and persistence of disseminated tumor cells (DTC) in the bone marrow of women with early-stage breast cancer [33]. In one study, women with detectable DTC in bone marrow at baseline were treated with ZOL (4 mg IV every month) for 2 years with concomitant endocrine therapy. At the 1-year follow-up, 69% of patients had a decrease in DTC compared with baseline ($p = 0.013$), and 71% had reduced DTC at 2 years ($p = 0.01$). In the second study, 172 patients with detectable tumor cells in bone marrow were randomized to adjuvant chemotherapy alone (control; $n = 141$) or in combination with ZOL (4 mg IV every 28 days; $n = 31$) for 6 months. After treatment, tumor cells were detected in the bone marrow of 27% of the patients in the control group

compared with 13% in the ZOL group ($p = 0.099$) [34]. In another study, 120 women with newly diagnosed breast cancer were randomized to neoadjuvant chemotherapy with or without ZOL (4 mg every 3 weeks) for 1 year. Of the women who were DTC-positive at baseline, 70% of ZOL-treated patients were DTC-negative at 3 months versus 53% in the chemotherapy-alone group ($p = 0.054$) [35]. In addition, 87% of ZOL-treated patients who were DTC-negative at baseline remained DTC-negative at 3 months versus 60% of patients receiving chemotherapy alone ($p = 0.03$). Another study in 45 patients who were DTC-positive after completing adjuvant chemotherapy recently reported outcomes after 49 months median follow-up. In this study, treatment with monthly ZOL for 2 years significantly reduced the prevalence of DTCs at 12 and 24 months versus baseline ($p \leq 0.001$) [36]. ZOL was well tolerated in each of these studies.

In a small trial in patients with advanced breast cancer ($n = 42$), a single dose of ZOL administered prior to chemotherapy reduced circulating levels of vascular endothelial growth factor (VEGF, a key stimulator of angiogenesis) by at least 25% compared with baseline in 59.5% of the patients [37]. Further analysis revealed that ZOL-mediated reduction in VEGF levels was associated with significant increases in the times to first SRE ($p = 0.0002$), progression of bone disease ($p = 0.0024$), and deterioration in performance status ($p = 0.035$).

The first demonstration of ZOL's anticancer effect in a large adjuvant trial came from ABCSG-12: This was a comparison of tamoxifen with anastrozole and endocrine therapy alone with endocrine therapy plus ZOL (4 mg IV every 6 months) in premenopausal women with early-stage endocrine-responsive breast cancer. The first efficacy results from this study showed that DFS outcomes at 47.8 months median follow-up were similar with tamoxifen and anastrozole (HR = 1.096; $p = 0.593$) in 1,803 women receiving ovarian suppression therapy with goserelin. However, the addition of ZOL to adjuvant endocrine therapy significantly improved DFS by 36% ($p = 0.012$) and recurrence-free survival (RFS) by 35% ($p = 0.014$) and produced a trend toward improved OS. In multivariate analysis, ZOL was a significant predictor of improved DFS (HR = 0.67; $p = 0.022$) and RFS (HR = 0.68; $p = 0.028$) [38]. Interestingly, reduction in recurrences because of ZOL treatment was not limited to bone metastases: recurrences were reduced at all sites in the ZOL groups. Moreover, ZOL treatment was well tolerated in this patient population: there were no confirmed cases of osteonecrosis of the jaw, and no renal toxicity was noted. Therefore, addition of ZOL to adjuvant endocrine therapy proved a generally well tolerated and effective means of improving clinical outcomes for premenopausal women with breast cancer. Overall, results from this large randomized trial indicate that addition of ZOL to adjuvant endocrine therapy not only prevents endocrine therapy-associated bone loss but also improves clinical outcomes in premenopausal women with early-stage breast cancer [39].

The Z-FAST, ZO-FAST, and EZO-FAST trials were designed to evaluate the efficacy of ZOL for prevention of AI-associated bone loss as well as disease progression in postmenopausal women with breast cancer. Integrated analysis of the Z-FAST and ZO-FAST trials (total $n = 1,667$) after the 12-month median follow-up demonstrated a significant decrease in disease recurrence in the upfront-ZOL arm (0.84% vs. 1.9% in the delayed-ZOL arm; $p = 0.0401$) [40]. The 24-month integrated analyses support these data: disease recurrence rates were 3.6% in the upfront ZOL arm versus 5.5% in the delayed ZOL arm (DFS HR = 0.573; $p = 0.0183$). Interestingly, patients receiving upfront ZOL had fewer breast cancer recurrence at skeletal and extraskeletal sites. This DFS benefit with upfront ZOL was maintained at 48 months follow-up (HR = 0.59; $p = 0.0175$), despite approximately 25% of patients initiating ZOL in the delayed group. In Z-FAST ($n = 602$) and E-ZO-FAST ($n = 527$), there were no significant differences in proportions of patients with DFS events for upfront versus delayed ZOL ($p = 0.6283$ after 61 months follow-up in Z-FAST, and $p = 0.1397$ after 36 months follow-up in E-ZO-FAST). These results suggest that Z-FAST and E-ZO-FAST are underpowered to detect DFS differences between treatment groups in this relatively low-risk patient population, especially given the trial design (i.e. 'rescue' therapy, which has resulted in up to one quarter of patients in the delayed arm initiating ZOL). Indeed, integrated analysis of Z-FAST and ZO-FAST (total $n = 1,667$) revealed significantly reduced disease recurrence as early as after 12 months median follow-up ($p = 0.0401$), and a 43% reduced risk of DFS events by Kaplan-Meier analysis at 24 months follow-up ($p = 0.0183$). Further analyses including DFS assessments censoring patients who initiated ZOL in the delayed arms may provide further insight into the effects of ZOL on disease recurrence in these trials.

An ongoing prospective trial in patients with stage II/III breast cancer (AZURE; $n = 3,360$) currently is evaluating a tapered dosing schedule of ZOL (monthly for 6 months, then quarterly for 2 years, then twice yearly for a total treatment duration of 5 years) [41]. Unlike the Z/ZO/E-ZO-FAST and ABCSG-12 trials, this study is not limited to hormone-respon-

sive breast cancer, and will evaluate ZOL combined with adjuvant chemotherapy as well as endocrine therapy. In a pre-specified subset analysis of patients who received neoadjuvant chemotherapy ($n = 205$), the addition of ZOL reduced the mean residual invasive tumor size by approximately 44% compared with chemotherapy alone (15.5 mm vs. 27.4 mm; $p = 0.006$). In addition, patients receiving neoadjuvant chemotherapy with ZOL had an approximately 2-fold increase in complete pathological remissions.

Conclusion and Perspectives for the Future

A large number of clinical trials have demonstrated the usefulness and safety of anti-resorptive drugs in the adjuvant treatment of postmenopausal women with endocrine-responsive breast cancer. BPs have shown that they can virtually eliminate CTIBL – they are therefore being included in current treatment guidelines despite the still existing lack of approval for this indication. In addition, particularly ZOL has demonstrated inherent anticancer activity in preclinical studies, and recent trial results indicate that addition of BPs to conventional adjuvant therapy at doses that prevent bone loss can significantly improve clinical outcomes in women with early-stage breast cancer. Several ongoing trials (AZURE, NSABP B-34, SWOG 0307, SUCCESS, NATAN, AZAC, ZEUS, RADAR, ABCSG-18, C-CARE) are further exploring the potential adjuvant benefits of BPs and denosumab in breast and other cancers, and will enroll nearly 20,000 patients. As data from these studies mature, the role of bone-directed therapy in oncology is likely to expand, particularly in the adjuvant setting.

Conflict of Interest

Dr. Gnant reports receiving research support from and serving as a consultant for AstraZeneca, Novartis, and Pfizer, and receiving lecture fees and honoraria for participation on advisory boards from AstraZeneca, Novartis, Sanofi-Aventis, Roche, Schering, Amgen, and Pfizer.

References

- 1 Garcia M, Jemal A, Ward EM, et al.: Global Cancer Facts and Figures, 2007. Atlanta, GA, American Cancer Society, 2007.
- 2 Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.
- 3 Winer EP, Hudis C, Burstein HJ, et al.: American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005;23:619–29.
- 4 Cummings SR, Browner WS, Bauer D, et al.: Endogenous hormones and the risk of hip and vertebral fractures among older women. For the Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1998;339:733–8.
- 5 Finkelstein JS, Brockwell SE, Mehta V, et al.: Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab* 2008;93:861–8.
- 6 Coleman R: Effect of anastrozole on bone mineral density: 5-year results from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. *J Clin Oncol* 2006;24(18S):5s(abstr 511).
- 7 Pfeilschifter J, Diel IJ: Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol* 2000;18:1570–93.
- 8 Shapiro CL, Manola J, Leboff M: Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol* 2001;19:3306–11.
- 9 Ellis GK, Bone HG, Chlebowski R, et al.: Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 2008;26:4875–82.

- 10 Saarto T, Vehmanen L, Blomqvist C, et al.: Ten-year follow-up of 3 years of oral adjuvant clodronate therapy shows significant prevention of osteoporosis in early-stage breast cancer. *J Clin Oncol* 2008;26:4289–95.
- 11 Delmas PD, Balena R, Confravreux E, et al.: Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol* 1997;15:955–62.
- 12 Hines SL, Mincey BA, Sloan JA, et al.: N02C1: a phase III randomized, placebo-controlled, double-blind trial of risedronate for prevention of bone loss in premenopausal women undergoing adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2008;26(suppl):12s(abstr 525).
- 13 Van Poznak C, Hannon RA, Clack G, et al.: The SABRE (study of anastrozole with the bisphosphonate risedronate) study: 12-month analysis. *Breast Cancer Res Treat* 2007;106(suppl 1):S37(abstr 502).
- 14 Singh S, Cuzick J, Edwards R, et al.: Effect of anastrozole on bone mineral density after one year of treatment: results from bone sub-study of the International Breast Cancer Intervention Study (IBIS-II). *Breast Cancer Res Treat* 2007;106(suppl 1):S9(abstr 28).
- 15 Lester JE, Dodwell D, Purohit OP, et al.: Use of monthly oral ibandronate to prevent anastrozole-induced bone loss during adjuvant treatment for breast cancer: two-year results from the ARIBON study. *J Clin Oncol* 2008;26(suppl):19s(abstr 554).
- 16 Brufsky A, Bundred N, Coleman R, et al.: Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008;13:503–14.
- 17 Schenk N, Lombart A, Frassolatti A, et al.: The E-ZO-FAST trial: zoledronic acid effectively inhibits aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Eur J Cancer Suppl* 2007;5:186(abstr 2008).
- 18 Hershman DL, McMahon DJ, Crew KD, et al.: Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 2008;26:4739–45.
- 19 Study to determine treatment effects of denosumab in patients with breast cancer receiving aromatase inhibitor therapy. *clinicaltrials.gov/ct2/show/NCT00556374*.
- 20 Mundy GR: Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2002;2:584–93.
- 21 Winter MC, Holen I, Coleman RE: Exploring the anti-tumour activity of bisphosphonates in early breast cancer. *Cancer Treat Rev* 2008;34:453–75.
- 22 Santini D, Martini F, Fratto ME, et al.: In vivo effects of zoledronic acid on peripheral gamma delta T lymphocytes in early breast cancer patients. *Cancer Immunol Immunother* 2009;58:31–8.
- 23 Gnant M: Bisphosphonates in the prevention of disease recurrence: current results and ongoing trials. *Curr Cancer Drug Targets* 2009;9:824–33.
- 24 Meads MB, Hazlehurst LA, Dalton W: The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance. *Clin Cancer Res* 2008;14:2519–26.
- 25 Gnant M: Bisphosphonates in the prevention of disease recurrence: current results and ongoing trials. *Current Cancer Drug Targets* 2009;9:824–33.
- 26 Powles T, Paterson A, McCloskey E, et al.: Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer. *Breast Cancer Res* 2006;8:R13.
- 27 Diel IJ, Solomayer EF, Costa SD, et al.: Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998;339:357–63.
- 28 Saarto T, Vehmanen L, Virkkunen P, et al.: Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. *Acta Oncol* 2004;43:650–6.
- 29 Ha TC, Li HM: Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* 2007;96:1796–801.
- 30 Zaghoul MS, Boutrus R, El-Hosieny H, et al.: A controlled prospective randomized placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer patients. *J Clin Oncol* 2008;26(suppl):257s(abstr 5033).
- 31 Morgan G, Davies F, Gregory W, et al.: Evaluating the effects of zoledronic acid (ZOL) on overall survival (OS) in patients (Pts) with multiple myeloma (MM): results of the Medical Research Council (MRC) Myeloma IX study. *J Clin Oncol* 2010;28(suppl):578s(abstr 8021).
- 32 Mystakidou K, Katsouda E, Parpa E, et al.: Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline. *Med Oncol* 2005;22:195–201.
- 33 Lin A, Park J, Melisko M, et al.: Zoledronic acid as adjuvant therapy for women with early stage breast cancer and occult tumor cells in bone marrow. *Breast Cancer Res Treat* 2007;106(suppl 1):S40(abstr 510).
- 34 Rack BK, Jueckstock J, Genss E-M, et al.: Effect of zoledronate on persisting isolated tumor cells in the bone marrow of patients without recurrence of early breast cancer. *Breast Cancer Res Treat* 2007;106(suppl 1):S40(abstr 511).
- 35 Aft R, Naughton M, Trinkaus K, et al.: Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial. *Lancet Oncol* 2010;11:421–8.
- 36 Greenberg S, Park JW, Melisko ME, et al.: Effect of adjuvant zoledronic acid (ZOL) on disseminated tumor cells (DTC) in the bone marrow (BM) of women with early stage breast cancer (ESBC): updated results. *J Clin Oncol* 2010;28(15s):(suppl; abstr 1002).
- 37 Vincenzi B, Santini D, Dicuonzo G, et al.: Zoledronic acid-related angiogenesis modifications and survival in advanced breast cancer patients. *J Interferon Cytokine Res* 2005;25:144–51.
- 38 Gnant M, Mlineritsch B, Schippinger W, et al.: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *New Engl J Med* 2009;360:679–91.
- 39 Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al.: Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol* 2008;9:840–9.
- 40 Coleman R, Bundred NJ, De Boer R, et al.: Impact of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST, ZO-FAST, and E-ZO-FAST (poster). Presented at: 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, 9–13 December 2009 (abstr 4082). www.posters2view.com/sabcs09/viewp.php?nu=4082.
- 41 Coleman RE, Winter MC, Cameron D, et al.: The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer* 2010;102:1099–105.