Pathol. Oncol. Res.
DOI 10.1007/s12253-012-9586-9

REVIEW

Bone Homeostasis and Breast Cancer: Implications for Complex Therapy and the Maintenance of Bone Integrity

Orsolya Rusz · Zsuzsanna Kahán

Received: 23 April 2012 / Accepted: 7 November 2012

Abstract The standard of care in bone metastases is antiresorptive therapy. If present in the bone, tumor cells induce a vicious cycle by stimulating the osteoclasts, which further accelerates tumor progression. The widely-used bisphosphonates or the new therapeutic option, denosumab an inhibitor of the receptor activator of NF-κB ligand (RANKL), interrupt this vicious cycle, inhibit tumor growth, and in clinical practice prevent skeleton-related events. Adjuvant oncological therapy, including chemotherapy and endocrine manipulations (ovarian ablation and tamoxifen in premenopausal, and aromatase inhibitors in postmenopausal women), increases the bone turnover and the risk of fracture. Awareness is essential for the diagnosis and treatment of cancer therapy-induced bone loss, or its prevention with appropriate calcium and vitamin D supplementation. A new possibility has been suggested for the prevention of relapse: the use of bisphosphonates in the adjuvant setting. Three large studies and their meta-analyses indicate that the inhibition of bone remodeling prevents the growth of dormant tumor cells and cancer relapse in the population of postmenopausal patients with a low-estrogen environment in the skeleton. The similar potential of a RANKL inhibitor is currently under evaluation. Since the maintenance of bone integrity is necessary for the prevention of both therapy-related side-effects and progression of the disease, the management of breast cancer at any stage requires a careful consideration of the bone homeostasis.

Keywords Breast cancer · Bisphosphonates · Denosumab · Bone · Prevention

O. Rusz · Z. Kahán (✉)
Department of Oncotherapy, University of Szeged,
Korányi fasor 12,
6720 Szeged, Hungary
e-mail: kahan.zsuzsanna@med.u-szeged.hu

Introduction

Since patients with breast cancer are at an increased risk of skeletal complications throughout the course of their disease, attention must be paid to maintaining the bone homeostasis. Interventions may promote the prevention of both therapy-related adverse events and tumor relapse. Thus, the everyday functioning, the quality of life, the cancer-free status and health economics are concerned when the topic of bone integrity is considered.

Anti-Bone Remodeling Therapy in Bone Metastasis

Around 70 % of advanced-stage breast cancer patients develop bone metastases. If these remain without therapy, they may result in debilitating skeletal events and a significant deterioration in the quality of life. Great advances have been achieved in the management of bone metastasis in breast cancer: since bisphosphonates and (more recently) denosumab an inhibitor of the receptor activator of the NF-κB ligand (RANKL), i.e. the bone-modifying agents, were shown to interact with both bone destruction and tumor progression, they have become an integral component of the complex therapy of bone metastases [1].

The development of tumor metastases in the skeleton is a complex multistep process. For tumor cell colonies to undergo successful implantation, a cross-talk between bone-resorbing osteoclasts and cancer cells is critical for the emergence of a microenvironment (the metastatic niche) suitable for acceptance of the micrometastases in the bone. In this abnormal microenvironment, the balance between the participants of the bone homeostasis is altered. A vicious cycle arises, and the bone and tumor cells mutually stimulate each other, which results in progression of the bone

Published online: 05 December 2012

metastases and bone remodeling. The recruitment and maturation of the osteoclasts is upregulated, though their attachment to the bone surface is critical for bone degradation. This also leads to activation of the osteoblasts. In bone metastases, therefore, enhanced remodeling takes place while the bone resorption and calcification are both activated. Bone metastases in breast cancer are osteolytic rather than osteoblastic. Among various osteolytic cytokines, the parathormone-related peptide has a crucial role in the pathomechanism of bone metastasis, since it stimulates the secretion of the RANKL responsible for osteoclast activation (Table 1) [2–4].

The recent progress in the understanding of the biological mechanism of bone metastasis led to the development of specific bone-targeted therapies that inhibit bone resorption. Bisphosphonates bind to the bone surface, and exert a direct toxic effect on the osteoclasts. The humanized RANKL antibody inhibits osteoclastogenesis by selectively targeting and neutralizing the RANKL.

The family of bisphosphonates contains molecules involving a P-C-P chain linked to variable side- chains, with different affinities for bone and different modes of action as regards osteoclast inhibition (Fig. 1, Table 2). In the bone, bisphosphonates bound to hydroxyapatite inhibit the dissolution of calcium phosphate and the activity of the osteoclasts. After their endocytosis, the bisphosphonates interact with various intracellular enzymatic steps. The mode of action depends on the type of the bisphosphonate: non-nitrogen-containing bisphosphonates are metabolized to cytotoxic nucleotide analogs in the osteoclasts, while nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase which is responsible for the prenylation of GTP-ases. Nitrogen-containing bisphosphonates inhibit mature osteoclasts and the migration and evolution of the premature osteoclasts. Although bisphosphonates inhibit enzymes that are present in all cells, their toxic effect is limited to osteoclasts because these cells accumulate bisphosphonates in sufficiently high concentration [5].

Table 1 Mediators that play a role in the vicious cycle that stimulates bone remodeling [2–4]

Mediator	Source/localization	Activity
VEGF-A	tumor cells	stimulates angiogenesis
FGF-1, FGF-2	stored in extracellular matrix	stimulates angiogenesis
VEGF-C, VEGF-D	tumor cells	stimulates lymphangiogenesis
M-CSF	mesenchymal stem cells, tumor cells	stimulates osteoclastogenesis
RANKL	osteoblasts	enhances the maturation, migration and activation of osteoclasts
PTHrP	tumor cells	increases the expression of RANKL decreases the expression of OPG
IGF-1	bone mass	enhances tumor cell proliferation, increases chemotaxis, prevents apoptosis
TGF-β	bone mass	enhances the production of PTHrP in tumor cells
PDGF	platelets	enhances tumor cell proliferation
BMP	bone mass	enhances tumor cell proliferation
OPN,BSP, vitronectin, collagen type-1	bone mass	increases tumor cell homing to bone
integrins	surface of tumor cells	increases tumor extravasation and binding to bone extracellular matrix (OPN, BSP, vitronectin)
SDF1	bone marrow	increases tumor cell homing to bone via interaction with CXCR4 receptor on tumor surface
IL-1	monocytes/macrophages	increases the expression of IL-6 and IL-11 in osteoblasts
IL-3	activated T-cells, macrophages	enhances the maturation of osteoclasts
IL-6, IL-11	osteoblasts, bone marrow stromal cells, tumor cells	enhances the maturation of osteoclasts
TNF-α,-β	monocytes/macrophages	increases the expression of IL-6 and IL-11 in osteoblasts
MMPs	extracellular matrix, tumor cells	increases tumor invasion and migration
cadherin-11, N-cadherin	cell membrane	increases tumor invasion and migration
E-cadherin	cell membrane	loss of E-cadherin is essential for tumor spreading
OPG	osteoblasts, hematopoietic cells	decoy receptor for RANKL, decreased level of OPG!

VEGF vascular endothelial growth factor; *FGF* fibroblast growth factor; *M-CSF* macrophage colony stimulating factor; *RANKL* receptor activator of NF-κB ligand; *PTHrP* parathyroid hormone-related protein; *IGF* insulin-like growth factor; *TGF-β* transforming growth factor; *PDGF* platelet-derived growth factor; *BMP* bone morphogenetic protein; *OPN* osteopontin; *BSP* bone sialoprotein; *SDF1* stromal cell-derived factor 1; *IL* interleukin; *TNF* tumor necrosis factor, *MMP* matrix metalloproteinase; *OPG* osteoprotegerin

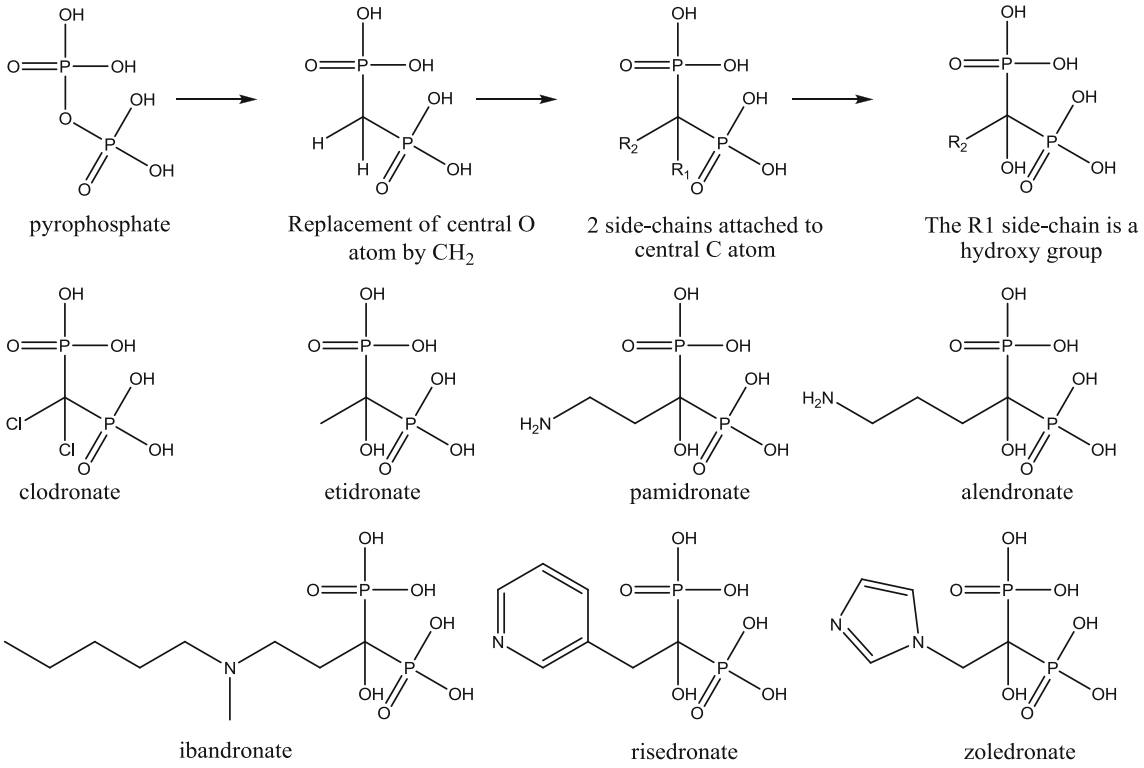


Fig. 1 Bisphosphonates: formation and structure

The following effects exerted by bisphosphonates result in disruption of the vicious cycle in bone metastasis [6, 7]:

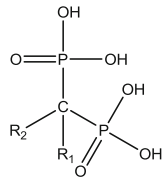
- They decrease the number of osteoclasts;
- They inhibit the binding of osteoclasts to the bone surface;
- They downregulate the expression of RANK in osteoclasts;
- They inhibit tumor cell adhesion to the bone surface;
- They inhibit angiogenesis; and
- They act synergistically with chemotherapy.

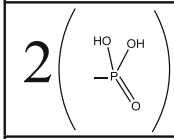
The absorption of oral bisphosphonates (only 1 %) is limited by the high pH in the small intestine. Their plasma concentration rapidly decreases within 1 h, and they bind to bone, especially where intense bone remodeling is taking place. Bisphosphonates are not metabolized, and are eliminated by the skeleton and the kidneys. Their half-lives are many years. Since the clearance of bisphosphonates depends on the kidney function, the dose must be modified accordingly (Fig. 2) [8]. Adverse effects are rare, and may be prevented by close surveillance (Table 3) [9].

A number of clinical studies have demonstrated the potential of bisphosphonates in the complex therapy of breast cancer bone metastases. Ross et al. reviewed 30 randomized trials in which bone metastatic breast cancer patients were treated with bisphosphonates. The administration of bisphosphonates for at least 6 months significantly reduced the occurrence of skeleton-related events (SREs), including fracture, the need for radiotherapy or surgery or myelon compression or hypercalcemia due to bone metastasis [10]. The meta-analysis of 9 randomized studies of 2,806 cases in which the bisphosphonate arm was compared with a control arm showed that bisphosphonates can reduce the risk of a SRE by 15 % (RR=0.85; 95 % CI 0.77–0.94; p=0.001) [11]. The use of bisphosphonates resulted in better pain reduction and an improved quality of life [12]. No effect on survival was demonstrated. Intravenously administered nitrogen-containing bisphosphonates are superior in preventing a SRE, and the most potent of all known bisphosphonates is zoledronate, a third-generation intravenous bisphosphonate (RR=0.59; 95 % CI 0.42–0.82) [11]. Two studies indicated the beneficial effects of reduced bone resorption and pain when the treatment of patients with progressive bone metastases or SREs was changed from clodronate to a third-generation bisphosphonate (ibandronate or zoledronate) [13, 14]. Bisphosphonates are generally well-tolerated; rare complications may be prevented by awareness of the possibility of a renal impairment or osteonecrosis of the jaw (Table 3) [1, 9, 15].

Denosumab is a fully humanized monoclonal IgG2 antibody that targets the RANKL, and provides an alternative method for the treatment of breast cancer bone metastases [16]. While the bisphosphonates interact with intracellular processes of the ostoclasts, denosumab blocks the extracellular process of RANK/RANKL signal transduction. The RANKL,

Table 2 Structure-activity relationship of bisphosphonates



Structure	Activity
	binds to bone and enzymes (farnesyl pyrophosphate synthase, aminoacyl-tRNA synthases)
P-C-P	metabolic and kinetic stability
R1: - hydroxy	chemical variability - increased binding affinity to bone
R2: - methyl or chloro - nitrogen-containing side-chain	chemical variability -inhibition of mitochondrial ATP metabolism (clodronate, etidronate) - improved inhibition of farnesyl pyrophosphate synthase and antiresorptive effect
primary amine	alendronate, pamidronate
tertiary amine	ibandronate
pyridine	risedronate
imidazole	zoledronate

produced by the osteoblasts, is a member of the TNF family, and enhances the maturation, migration and activity of osteoclasts. After binding to the RANKL, denosumab neutralizes it, thereby inhibiting bone resorption by blocking premature and mature osteoclasts [17]. Denosumab is administered as a subcutaneous injection. After its rapid absorption, the peak plasma concentration (C_{max}) is obtained after 7–14 days. Complete elimination by the reticuloendothelial system (as in the case of other antibodies) takes around 6 months, and is not influenced by the renal or hepatic function. If there is a renal insufficiency, the serum calcium level should be monitored. No antibody against denosumab is produced after its administration. [18]

In a large phase III study involving 2,046 breast cancer cases with bone metastases, denosumab was tested against intravenous zoledronate. Denosumab significantly delayed the time to the first (HR=0.82, p=0.01) or subsequent SREs (HR=0.77, p=0.001). No difference in overall survival or disease progression was found between the treatment arms. While significantly more chills, pyrexia, bone pain and arthralgia occurred in the zoledronate arm, more hypocalcemia developed among the denosumab-treated patients [19]. During denosumab therapy, vigilance is needed in order to the prevent hypocalcemia, especially in patients with an impaired renal function (Tables 3 and 4) [1]. The study

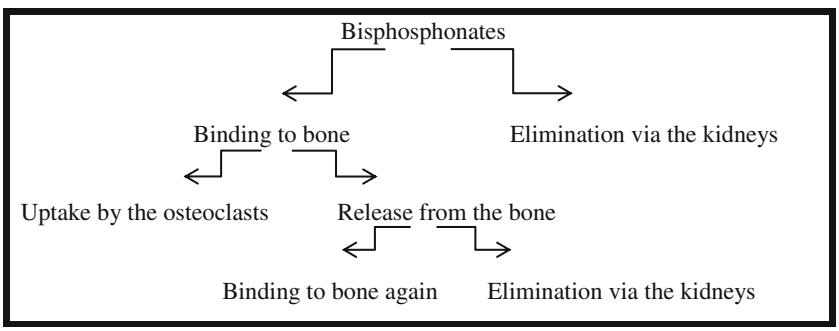


Fig. 2 The metabolism of bisphosphonates

Table 3 Possible toxic effects of bisphosphonates and their prevention

Adverse event	Risk reduction	Risk factor
- nausea, vomiting, dyspepsia (oral BPs) - esophagitis, esophageal erosion (oral BPs) - esophageal cancer (oral BPs)	oral administration: instructions for administration or change for intravenous administration	anamnestic GI hemorrhage, peptic ulcer, Barrett esophagus
- conjunctivitis (iv. BPs) - uveitis, iriditis (iv. BPs)	mild and transient; all ophthalmic symptoms should be monitored	
- renal toxicity (iv. BPs)	kidney function should be regularly monitored	chemotherapy, diabetes, previous kidney lesion
- hypocalcemia (iv. or oral BPs)	serum Ca monitoring	
- acute phase reaction (only iv. nitrogen-containing BPs)	paracetamol therapy	
- atrial fibrillation	follow-up of patients at risk	
- muscle pain		
- osteonecrosis of the jaw (ONJ)	avoidance of invasive dental intervention	poor oral hygiene
- atypical fracture		

BPs bisphosphonates, *iv* intravenous

contributed to the registration of denosumab for the prevention of SRE in bone metastatic solid tumors. Long-term efficacy and safety data are awaited.

In conclusion, anti-bone remodeling therapy with bisphosphonates or with denosumab is recommended for breast cancer patients with bone metastases. All such patients should be examined at the commencement of therapy, and regularly monitored thereafter for maintenance of the optimal level of oral health and renal function. The follow-up of biochemical markers of bone remodeling is not justified (Table 4).

The Prevention of Adjuvant Breast Cancer Therapy-Induced Bone Loss

Adjuvant therapy, including adjuvant endocrine therapy and chemotherapy, is extensively applied postoperatively with curative intent. Both forms of intervention increase the risk of bone loss and bone fracture [20].

Since estrogens play a key role in the development and progression of hormone-sensitive breast cancer, the common goal of the currently applied endocrine manipulations is estrogen deprivation, either by competitive blockade of the hormone at the level of its receptor or by inhibition of its synthesis. Adjuvant endocrine therapy lasts for many years, and there is therefore sufficient time for the development of side-effects and long-term sequelae of the therapy.

Osteoporosis, a progressive natural process associated with a yearly 1 % decrease in bone mineral density (BMD) and a higher risk of fracture in postmenopausal women, is accelerated by an estrogen deficiency. Tamoxifen exerts differential effects on the BMD, depending on the menopausal status: in premenopausal women, it causes a significant lowering of the BMD, whereas in postmenopausal patients it improves both

Table 4 ASCO guidelines on the role of bone-modifying agents (BMAs) in metastatic breast cancer [1]

- BMAs are recommended for patients with metastatic breast cancer with evidence of bone destruction
- Denosumab 120 mg subcutaneously every 4 weeks; intravenous pamidronate 90 mg over no less than 2 h every 3 to 4 weeks; or intravenous zoledronic acid 4 mg over no less than 15 min every 3 to 4 weeks
- One BMA is not recommended over another
- In patients with a creatinine clearance of 60 mL/min, no change in dosage, infusion time or interval is required; the creatinine level is monitored for each intravenous bisphosphonate dose
- In patients with a creatinine clearance of 30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended
- All patients should have a dental examination and preventive dentistry before using a BMA
- At the onset of cancer bone pain, the standard of care for pain management should be provided and BMAs should be started
- The use of biochemical markers to monitor BMA use is not recommended for routine care

spongious (spine) and compact (hip) bone formation [21]. Significant increases in BMD were demonstrated in different studies after the administration of tamoxifen to postmenopausal breast cancer patients [22, 23].

Adjuvant aromatase inhibitor (AI) therapy brings about a long-lasting significant deprivation of circulatory and tissue estrogens. As a result, the fall in BMD is enhanced to about 2.5 % per year [24, 25]. In the bone subprotocol of the ATAC study, patients treated with anastrozole exhibited significant decreases in BMD (~ 4 %), whereas those treated with tamoxifen displayed significant BMD increases of 1.2 % and 2.2 % in the lumbar and hip areas, respectively [25]. Significantly more new osteoporosis was observed among the AI-treated women in the IES and MA. 17 trials [25–27]. In the adjuvant AI studies, fracture rates were consistently elevated in the AI arms as compared with the tamoxifen arms, but the differences disappeared after the termination of therapy in the ATAC study [28].

Ovarian ablation, achieved either surgically or medically, causes a significant depletion of sex hormones in premenopausal women. The application of LHRH analogs results in transient, but complete ovarian hormone ablation, which is usually maintained for up to 2–3 years. In the bone subprotocol of the ZEBRA study, the mean BMD losses in premenopausal patients treated with goserelin for 2 years were 10.5 % and 6.4 % for the lumbar spine and femoral neck, respectively. At 3 years, in contrast with the situation after CMF (cyclophosphamide, methotrexate and 5-fluorouracil) chemotherapy, a partial recovery was seen [29]. Chemotherapy-induced amenorrhea develops in a transient or definitive manner, depending on the age of the patient and the regimen applied [20]. The impact of chemotherapy on bone loss is probably mediated mostly by ovarian ablation, though the direct effects of cytostatic agents on the bone homeostasis can not be excluded.

Arthralgia is a typical adverse event of estrogen deprivation that is most significant during AI therapy. The arthralgia syndrome includes not only joint pain, but also myalgia, fibromyalgia or neuropathy, and its incidence may be as high as 50 % among patients on AI therapy [30, 31]. This syndrome results in a decreased mobility of the patient, another factor enhancing the risk of increased bone loss.

The available data suggest that bisphosphonates have the potential to prevent bone loss during adjuvant breast cancer therapy [32] (Table 5). The oral bisphosphonate risedronate has been found to be effective in preventing chemotherapy-induced bone loss in premenopausal women [33]. In the Z-FAST study, 602 postmenopausal patients receiving adjuvant letrozole therapy were randomized to upfront vs. delayed zoledronate therapy (in the delayed group therapy was started if the BMD decreased to −2.0) [36]. In the companion studies ZO-FAST and E-ZO-FAST, similar results were found, despite the fact that the 3 studies included patients from different geographical areas [37, 38]. In the ABCSG-12 trial, the BMD was studied in premenopausal women treated with goserelin and either tamoxifen or anastrozole, with or without zoledronate. During the administration of goserelin plus tamoxifen or anastrozole as adjuvant hormone therapy for 3 years, the BMD of the lumbar spine decreased by 9.0 % (tamoxifen) or by 13.6 % (anastrozole) in the absence of bisphosphonate therapy. Although the BMD of the lumbar spine had to some extent recovered 2 years after the discontinuation of therapy, it was still below the baseline in both groups, despite the fact

Table 5 Studies for the prevention of adjuvant therapy-induced bone loss

	Patients	Oncological therapy	Bisphosphonate	BMD change
Delmas et al. 1997 [33]	*n*=53, premeno	chemotherapy	risedronate 35 mg/week vs. placebo	0.3 vs. −1.4 % per year
Lester 2007, ARIBON [34]	*n*=131, postmeno	anastrozole	ibandronate vs. placebo	2.8 vs. −2.6 % per year
Gnant 2011, ABCSG-12 subgroup [35]	*n*=401, premeno	goserelin + anastrozole or goserelin + tamoxifen	zoledronate 4 mg/ 6 months vs. nil	NC vs. −17.4 or −11.6 % per 3 years
Brufsky 2011, Z-FAST [36]	*n*=602	letrozole	zoledronate 4 mg/6 months upfront vs. delayed	1.9 vs. −2.5 % per year
Eidtmann 2009, ZO-FAST [37]	*n*=1066	letrozole	zoledronate 4 mg/6 months upfront vs. delayed	4.4 vs. −4.9 % per 5 years
Llombart 2012, E-ZO-FAST [38]	*n*=527	letrozole	zoledronate 4 mg/6 months upfront vs. delayed	2.7 vs. −2.7 % per year
Hines 2009, N03CC [35]	*n*=395	extended adjuvant letrozole	zoledronate 4 mg/6 months upfront vs. delayed	3.7 vs. −1.7 % per year
van Poznak 2010, SABRE [39]	*n*=111	anastrozole	risedronate 35 mg/ week vs. placebo	significant increase vs. decrease in 3 risk groups
Ellis 2008, HALT-BC [40]	*n*=252	aromatase inhibitor	denosumab 60 mg/ 6 months vs. placebo	6.2 vs. −1.4 % per 2 years

BMD bone mineral density

Table 6 Adjuvant bisphosphonate therapy in breast cancer

Study	n	Schedule	FU	HR overall	HR postmenopausal subgroup
Powles 2004 [46]	1069	clodronate 1,600 mg, 2 years	5 years	0.692 (p=0.043) (bone)	
Diel 1998 [47]	302	clodronate 1,600 mg, 2 years	53 months	p<0.001	
ABCSG-12 [35]	3360	zoledronate 4 mg, 6 months	5 years	0.68 (p=0.009)	NA
AZURE [48]	3539	zoledronate 4 mg, 1-3-6 months	59 months	NS	0.76 (p<0.05)
Z-FAST [36]	602	zoledronate 4 mg, 6 months	54 months	NS	NA
ZO-FAST [37]	1066	zoledronate 4 mg, 6 months	48 months	0.66 (p=0.0375)	NA
E-ZO-FAST [38]	527	zoledronate 4 mg, 6 months	59 months	NS	NA

FU follow-up, *HR* hazard ratio, *NS* not significant; *NA* not appropriate

that three-quarters of the patients had regained menses [35, 41–43]. Similarly, a significantly increased BMD was attained in the N03CC study, in which zoledronate was applied together with extended adjuvant letrozole therapy after 5 years of tamoxifen [39], and in the SABRE study, in which risedronate was applied together with anastrozole, as compared with these endocrine agents together with placebo [40]. In the Hormone Ablation Bone Loss Trial in Breast Cancer (HALT-BC) study, denosumab administered to patients on adjuvant AI therapy twice a year resulted in consistent increases in BMD at 12 and 24 months as compared with the placebo group [44].

A decreased BMD is the most important factor leading to an enhanced risk of fracture, an event with serious consequences to personal life and health economics. Other clinical risk factors, such as a reduced body mass index (BMI), a family or personal history of fracture, the use of corticosteroids and smoking should also be assessed prior to the initiation of breast cancer therapy with possible consequences to the bone homeostasis. Various guidelines exist with algorithms to evaluate individual fragility profile and treatment with antiresorptive therapy [45]. These are in accord as concerns the assumption of all risk factors, but recommend intervention with different agents and at different BMD thresholds.

In conclusion, adjuvant treatment in breast cancer may exert an adverse effect on the BMD and the risk of fracture, which should be monitored during therapy. Estrogen deprivation in particular should be handled with care at the start of the treatment and regularly thereafter. Long-term results with bisphosphonates and the promising data with denosumab indicate that their administration support the integrity of the bone by maintaining or even improving it during adjuvant endocrine therapy.

Adjuvant Anti-Bone Resorptive Therapy for the Prevention of Relapse in High-Risk Breast Cancer Patients

As previously detailed, during bone degradation and active bone remodeling, various growth factors and enzymes are released which may support the growth of tumor cells and the progression of the cancer. Hence, the blockade of this complex process by bone-targeted anti-resorptive agents is expected to inhibit cancer growth. The rate of bone loss is dramatically accelerated by ovarian ablation in premenopausal women and AI therapy in postmenopausal women. Both preclinical and clinical research data point to the possible tumor inhibitory effects of anti-bone resorptive agents (Table 6).

In two pilot studies involving high-risk breast cancer patients, disseminated tumor cells were cleared from the bone marrow by the administration of zoledronate [47]. Two early studies with a long follow-up demonstrated significant disease-free survival (DFS) and overall survival (OS) benefit after adjuvant clodronate therapy [47, 49]. The AZURE study evaluated the effects of zoledronate combined with chemotherapy and hormone therapy in a population of premenopausal and postmenopausal women [48]. In the overall study population there was no difference in DFS, whereas OS indicated a trend toward a better outcome in patients treated with zoledronate. Nonetheless, prospective subgroup analysis

Table 7 Clinical studies on bisphosphonates as breast cancer prevention therapy

Study	Design	Therapy	Breast cancer risk
Breast cancer Northern Israel Study (Rennert 2010 [54])	case–control study, n=4039 >50-year-old postmenopausal women	bisphosphonate >1 year (mostly alendronate)	0.72 (0.57−0.90)
WHI (Chlebowski 2010 [55])	WHI cohort, n=2816 bisphosphonate user/total n=154768 >50-year-old women	clodronate/alendronate, *FU*=93 months	0.70 (0.52−0.94) ER + BC: 0.68 (0.52−0.88)

FU follow-up

according to the menopausal status revealed a significant benefit of zoledronate in terms of DFS and OS if the patient had passed the menopause at least 5 years before the commencement of therapy. Within the AZURE study, 205 patients received neoadjuvant chemotherapy with or without zoledronate [50]. In this subgroup analysis, the primary endpoint was the residual invasive tumor size after surgery. The patients in the zoledronate arm exhibited a significantly greater response to treatment.

The ABCSG-12 study was designed to investigate the effects of zoledronate on survival in a population of 1,803 premenopausal breast cancer patients treated with combined endocrine therapy with or without zoledronate. The primary endpoint was a DFS. The administration of zoledronate was associated with a 32 % improvement in DFS after a follow-up time of 5 years, and interestingly, all distant metastasis sites and also locoregional recurrence rates were decreased by the intervention. The benefit in OS reached statistical significance after a median follow-up time of 76 months [35].

The aim of the Z-FAST, ZO-FAST and E-ZO-FAST companion trials was to evaluate the potential of zoledronate to prevent AI-induced bone loss in postmenopausal patients treated with letrozole. Among these studies, only the ZO-FAST trial, which was appropriately powered to detect a significant difference in events between the treatment arms, revealed such a potential (Table 6).

The randomized controlled adjuvant zoledronate studies were subjected to meta-analysis by Yan et al. [51]. This demonstrated that, while adjuvant zoledronate did not improve the survival in the overall population, in the subgroup of postmenopausal patients the addition of zoledronic acid to the standard therapy improved DFS, and decreased the risk of distant or locoregional recurrence (RR=0.763, $p<$ 0.001, RR=0.744, p=0.003, RR=0.508, p=0.001, respectively). The anticancer activity zoledronate is restricted to patients with a low estrogen level: the inhibition of enhanced bone remodeling results in the blockade of cancer stimulation. Accordingly, the monoclonal antibody denosumab, which is also able to influence the bone microenvironment, is under investigation as potential adjuvant therapy in high-risk breast cancer patients (Table 6) [52].

Breast Cancer Prevention

The prevention of breast cancer in healthy individuals implies intervention in those at high risk of developing breast cancer. Besides life style changes and diet, the options studied for prevention include medical therapy traditionally referred to as called chemoprevention, but the expression breast cancer prevention has recently been concluded to be more appropriate nomenclature [53]. The medical therapy that has been studied includes the anti-estrogens, the estrogen depletion methods, e.g. involving AIs or LHRH analogs, the statins, the COX-2 inhibitors, metformin and the bisphosphonates.

Two relatively large studies that made use of pharmacy records or data from self-questionnaires in populations undergoing breast screening showed that in patients treated with bisphosphonates, the risk of breast cancer was reduced by about 30 % (Table 7). One study suggested a reduction in the number of estrogen receptor-negative breast cancers [54], and the other a reduction in the number of estrogen receptor-positive breast cancers [55]; the difference may be a result of differences in lifestyle and genetics between the two populations. These results are in consistence with those which point to bisphosphonates' direct antitumor activity. This potential could be more fully utilized if the rapid clearance of bisphosphonates from the circulation due to their pharmacokinetic features were prevented. New nanotechnology formulations such as liposomal and pegylated liposomal zoledronate show enhanced tumor inhibitory effects. In addition to the long-lasting presence of zoledronate resulting in higher extraskeletal bioavailability, the size of the nanoparticles favoring selective uptake by the tumor might explain increased efficiency [56, 57].

References

1. Van Poznak CH, Temin S, Yee GC et al (2011) American society of clinical oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol 29:1221–1227
2. Guise T (2010) Examining the metastatic niche: targeting the microenvironment. Semin Oncol 37:S2–S14
3. Yoneda T, Hiraga T (2005) Crosstalk between cancer cells and bone microenvironment in bone metastasis. Biochem Biophys Res Commun 328:679–687
4. Karen MB, Carol VG, Andrea MM (2008) The bone microenvironment in metastasis; what is special about bone? Cancer Metastasis Rev 27:41–55
5. Rogers MJ, Crockett JC, Coxon FP, Mönkkönen J (2011) Biochemical and molecular mechanisms of action of bisphosphonates. Bone 49:34–41
6. Clézardin P, Benzaïd I, Croucher PI (2011) Bisphosphonates in preclinical bone oncology. Bone 49:66–70
7. Kimachi K, Kajiya H, Nakayama S et al (2011) Zoledronic acid inhibits RANK expression and migration of osteoclast precursors during osteoclastogenesis. N Schmied Arch Pharmacol 383:297–308
8. Serge C, Socrates P (2011) Pharmacology of bisphosphonates. Bone 49:42–49
9. Arboleya L, Alperi M, Alonso S (2011) Adverse effects of bisphosphonates. Rheumatol Clin 7:189–197
10. Ross JR, Saunders Y, Edmonds PM et al (2003) Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. BMJ http://www.bmj.com/content/327/7413/469. Accessed 30 August 2003
11. Wong MHF, Stockler MR, Pavlakis N (2012) Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003474.pub3/full. Accessed 30 April 2011

12. Costa L, Major PP (2009) Effect of bisphosphonates on pain and quality of life in patients with bones metastases. Nat Clin Pract Oncol 6:163–174
13. Clemons M, Dranitsaris G, Ooi W, Cole DEC (2008) A phase II trial evaluating the palliative benefit of second-line oral ibandronate in breast cancer patients with either a skeletal related event (SRE) or progressive bone metastases (BM) despite standard bisphosphonate (BP) therapy. Breast Canc Res Treat 108:79–85
14. Clemons MJ, Dranitsaris G, Ooi WS et al (2006) Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. J Clin Oncol 24:4895–4900
15. Hillner BE, Ingle JN, Chlebowski RT et al (2003) American society of clinical oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21:4042–4057
16. Santini D, Fratto ME, Vincenzi B et al (2009) Denosumab: the era of targeted therapies in bone metastatic disease. Curr Canc Drug Targets 9:834–842
17. Baron R, Ferrari S, Russell RGG (2011) Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 48:677–692
18. Kumagai Y, Hasunuma T, Padhi D (2011) A randomized, double-blind, placebo-controlled, single-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of denosumab administered subcutaneously to postmenopausal Japanese women. Bone 49:1101–1107
19. Stopeck AT, Lipton A, Body JJ et al (2010) Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 28:5132–5139
20. Bjarnason NH, Hitz M, Jorgensen NR, Vestergaard P (2008) Adverse bone effects during pharmacological breast cancer therapy. Acta Oncol 47:747–754
21. Powles TJ, Hickish T, Kanis JA et al (1996) Effect of tamoxifen on bone mineral density measured by dual-energy X-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 14:78–84
22. Love RR, Mazess RB, Barden HS et al (1992) Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 326:852–856
23. Kristensen B, Ejlertsen B, Dalgaard P et al (1994) Tamoxifen and bone metabolism in postmenopausal low-risk breast cancer patients: a randomized study. J Clin Oncol 12:992–997
24. Geisler J, Lonning PE, Krag LE et al (2006) Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: a randomised, placebo-controlled study. Eur J Cancer 42:2968–2975
25. Perez EA, Josse RG, Pritchard KI et al (2006) Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA. 17. J Clin Oncol 24:3629–3635
26. Coombes RC, Kilburn LS, Snowdon CF et al (2007) Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 369:559–570
27. Coleman RE, Banks LM, Girgis SI et al (2007) Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol 8:119–127
28. Eastell R, Hannon RA, Cuzick J et al (2006) Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the anastrozole, tamoxifen, alone or in combination (ATAC) trial. J Bone Miner Res 21:1215–1223
29. Fogelman I, Blake GM, Blamey R et al (2003) Bone mineral density in premenopausal women treated for node-positive early breast cancer with 2 years of goserelin or 6 months of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Osteoporos Int 14:1001–1006
30. Crew KD, Greenlee H, Capodice J et al (2007) Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 25:3877–3883
31. Fontaine C, Meulemans A, Huizing M et al (2008) Tolerance of adjuvant letrozole outside of clinical trials. Breast 17:376–381
32. Hadji P, Bundred N (2007) Reducing the risk of cancer treatment-associated bone loss in patients with breast cancer. Semin Oncol 34:S4–S10
33. Delmas PD, Balena R, Confravreux E et al (1997) 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 15:955–962
34. Lester JE, Dodwell D, Purohit OP et al (2008) Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. Clin Cancer Res 14:6336–6342
35. Gnant M, Mlineritsch B, Stoeger H et al (2011) Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncol 12:631–641
36. Brufsky AM, Harker WG, Beck JT (2012) Final 5-year results of Z-FAST trial. Cancer 118:1192–1201
37. Eidtmann H, de Boer R, Bundred N et al (2010) Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST study. Ann Oncol 21:2188–2194
38. Llombart A, Frassoldati A, Paija O et al (2012) Immediate administration of zoledronic acid reduces aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. Clin Breast Canc 12:40–48
39. Hines SL, Mincey B, Dentchev T et al (2009) Immediate versus delayed zoledronic acid for prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen-N03CC. Breast Canc Res Treat 117:603–609
40. Van Poznak C, Hannon RA, Mackey JR et al (2010) Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. J Clin Oncol 28:967–975
41. Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al (2007) Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. J Clin Oncol 25:820–828
42. Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al (2008) 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 9:840–849
43. Gnant M, Mlineritsch B, Schippinger W et al (2009) Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 360:679–691
44. Ellis GK, Bone HG, Chlebowski R et al (2009) Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study. Breast Canc Res Treat 118:81–87
45. Hadji P, Aapro MS, Body JJ et al (2011) Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. Ann Oncol 22:2546–2555
46. Powles T, Paterson A, McCloskey E et al (2006) Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. Breast Canc Res 8:R13

47. Coleman RE (2009) Adjuvant bisphosphonates in breast cancer: are we witnessing the emergence of a new therapeutic strategy? Eur J Cancer 45:1909–1915
48. Coleman RE, Marshall H, Cameron D et al (2011) Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med 365:1396–1405
49. Diel IJ, Solomayer EF, Costa SD et al (1998) Reduction in new metastases in breast cancer with adjuvant clodronate treatment. N Engl J Med 339:357–363
50. Coleman RE, Winter MC, Cameron D et al (2010) 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 102:1099–1105
51. Yan T, Yin W, Zhou Q et al (2012) The efficacy of zoledronic acid in breast cancer adjuvant therapy: a meta-analysis of randomised controlled trials. Eur J Cancer 48:187–195
52. Lee BL, Higgins MJ, Goss PE (2012) Denosumab and the current status of bone-modifying drugs in breast cancer. Acta Oncol 51:157–167
53. Cuzick J, DeCensi A, Arun B et al (2011) Preventive therapy for breast cancer: a consensus statement. Lancet Oncol 12:496–503
54. Rennert G, Pinchev M, Rennert HS (2010) Use of bisphosphonates and risk of postmenopausal breast cancer. J Clin Oncol 28:3577–3581
55. Chlebowski RT, Chen Z, Cauley JA et al (2010) Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol 28:3582–3590
56. Marra M, Salzano G, Leonetti C et al (2012) New self-assembly nanoparticles and stealth liposomes for the delivery of zoledronic acid: a comparative study. Biotechnol Adv 30:302–309
57. Salzano G, Marra M, Porru M et al (2011) Self-assembly nanoparticles for the delivery of bisphosphonates into tumors. Int J Pharm 403:292–297