Review Article

Bone-modifying Agents (BMAs) in Breast Cancer

Charles L. Shapiro

Abstract

Bone-modifying agents (BMAs) are mainstays in breast cancer and prevent and treat osteoporosis in early-stage disease and reduce skeletal metastases complications in advanced disease. There is some evidence to support that BMA also prevents skeletal metastases and improves overall survival. Bone loss occurs with chemotherapy-induced ovarian failure, gonadotrophin-releasing hormone (GnRH) agonists, and aromatase inhibitors. In some women, the bone loss will be of sufficient magnitude to increase the risks of osteoporosis or fractures. Recommended steps in osteoporosis prevention or treatment include risk factor assessment, taking adequate amounts of calcium and vitamin D3, and periodic evaluations with dual-energy x-ray absorptiometry scanning. If clinically indicated by the T-scores and fracture-risk prediction algorithms treat with oral, IV bisphosphonates or subcutaneous denosumab (DEN). Zoledronic acid (ZA) or DEN reduces skeletal metastases complications, including pathological fracture, spinal cord compression, or the necessity for radiation or surgery to bone. Also, both of these drugs have the side-effect of osteonecrosis at a similar incidence. Monthly administration of ZA or DEN is standard, but several recent randomized trials show noninferiority between ZA monthly and every 3-month ZA. Every 3-month ZA is a new standard of care. Similar trials of the schedule of DEN are ongoing. ZA anticancer effect is only in postmenopausal women or premenopausal women rendered postmenopausal by GnRH agonists or bilateral oopherectomy. High-risk women, either postmenopausal or premenopausal, receiving GnRH/oopherctomy should consider adjuvant ZA. There are insufficient data to support DEN in this setting. Herein, this narrative review covers the mechanism of action of BMA, randomized clinical trials, and adverse events, both common and rare.

Clinical Breast Cancer, Vol. 000, No.xxx, 1–13
Keywords: Bone metastases, Denosumab, Osteoporosis, Zoledronic acid, Aromatase Inhibitors

Oral and Intravenous Bisphosphonates and RANK Ligand Inhibitor

N-amino bisphosphonates (Figure 1) cause osteoclast apoptosis, inhibition of osteoclast function by interfering in the differentiation of hematopoietic precursors into multinucleated giant cells, and binding of the osteoclasts to the bone surface.[1-3] The N-amino bisphosphonates are analogs of inorganic pyrophosphate, one of the bone mineral matrix primary components. The osteoclasts take up n-amino bisphosphonates in which they inhibit several steps in the post-translational modifications of guanosine triphosphate (GTP)-binding proteins Rab, Rac, and Rho. Osteoclastic resorption requires these GTP-binding proteins.[4] The less potent non-nitrogen bisphosphonates, clodronate and etidronate, are analog adenosine triphosphate that cause osteoclast apoptosis.[5] Clodronate is not approved in the United States but is approved in Europe.

Denosumab (DEN) is a humanized monoclonal antibody directed against receptor activator of nuclear factor-kappa B ligand (RANKL).[6] Inactivating RANKL prevents the binding of RANKL to the RANKL receptor, which is essential for osteoclast differentiation and activation. Zoledronic acid (ZA) and DEN differ in their mechanisms of action, pharmacokinetics, administration, costs, and cost-effectiveness (Table 1).[3,7-10]

Osteoporosis

Osteoporosis is an aging disease; approximately 1 in 3 postmenopausal women will experience an osteoporotic (or fragility) fracture of the hip, spine, or wrist.[11] Breast cancer is also a disease of aging. Most of the "1 in 8" lifetime risks of breast cancer are in women in their sixth, seventh, eighth, and ninth decades. Treatments for breast cancer, such as gonadotrophin-releasing hormone (GnRH) agonists, chemotherapy-induced ovarian failure (CIOF), and aromatase inhibitors (AIs), cause bone loss and increase the osteoporosis risks. Osteoporosis and breast cancer, 2 common and age-related conditions, make osteoporosis relevant in women with breast cancer throughout the continuum from diagnosis, treatment, and survivorship.[12]

Mechanisms of Action of Normal Bone and the Pathophysiology of Bone Loss/Osteoporosis

Heathy bone undergoes a dynamic process of bone resorption and new bone formation. Regulation of this process occurs in 2 ways.

Icahn School of Medicine at Mt Sinai, New York, NY

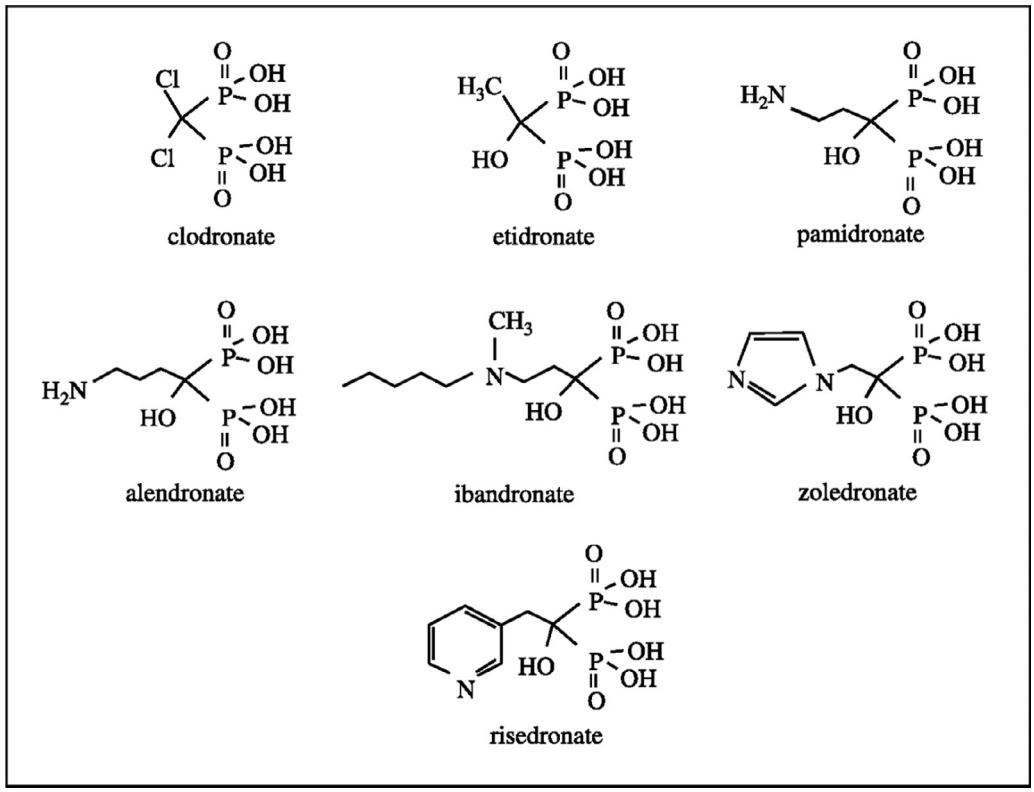
Submitted: Mar 11, 2021; Revised: Apr 19, 2021; Accepted: Apr 20, 2021; Epub: xxx

Address for correspondence: Charles L. Shapiro, MD, FASCO, Icahn School of Medicine at Mt Sinai, One Gustave Levy Place, Box 1079, New York, NY 10029.
E-mail contact: charles.shapiro@mssm.edu

1526-8209/$ - see front matter
https://doi.org/10.1016/j.clbc.2021.04.009

Please cite this article as: Charles L. Shapiro, Bone-modifying Agents (BMAs) in Breast Cancer, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2021.04.009

Figure 1 Structures of the bisphosphonates. The structures of non-nitrogen-containing (etidronate and clodronate¶) and nitrogen-containing (oral-alendronate, ibandronate, and risedronate; intravenous pamidronate and zoledronic acid) bisphosphonates. ¶Not available in the United States. Used with permission and modified from Roelofs AJ, et al. Molecular mechanisms of action of bisphosphonates: current status. *Clin Cancer Res* 2006; 12:6222s-30s.



One way includes mechanical forces of gravity, sex-steroid hormones (eg, androgens and estrogens), calcium regulating hormones (eg, parathyroid hormone [PTH], calcitonin, and calcitriol), and others (eg, insulin-like growth factor, thyroid hormone, and cortisol).[13] The other level is the bone remodeling unit with 3 primary cell types, osteocytes, osteoclasts, and osteoblasts.

Osteocytes serve as the source of nuclear factor kß ligand (RANKL) and osteoprotegerin (OPG) of the TNF receptor superfamily.[14] The binding of RANKL to the RANKL receptor causes osteoclast precursor cells, derived from hematopoietic cells, to differentiate into mature osteoclasts and resorb bone.[15] OPG serves as a decoy receptor for the RANKL, thus inhibiting bone resorption. The osteocytes release RANKL and other osteoclastic cytokines (ie, interleukin (IL)-1, IL-6, IL-7, IL-8, and IL-11) responsible for osteoclast differentiation and bone resorption.[16] Osteoblasts, derived from mesenchymal origin, are responsible for new bone formation via Wnt signaling that increases gene expression and enhances osteoblast survival.[14] Also, the osteocytes secrete sclerostin. Sclerostin suppresses Wnt signaling, which is critical for osteoblast function. Simply stated, it is the ratio of OPG to RANKL that governs bone resorption and bone formation.

T-cells, osteoblasts, and osteoclasts contain estrogen receptors (ER), both ER-α and ER-ß.[17] Estrogens preserve bone by causing osteoblast activation and differentiation, whereas estrogen deficiency causes osteoclast apoptosis.[18,19] Normal menopause or some breast cancer treatments (eg, oophorectomy, GnRH agonists, CIOF, or AIs) cause estrogen deficiency and net bone resorption. T regulatory cells secrete tumor necrosis factor-α, RANKL, and other proinflammatory cytokines that stimulate osteoclastic activity. CD8-positive T cells promote osteoblastic activity and inhibit bone resorption.[20,21]

Osteoporosis is akin to an equation.[22] On one side of the equation is the peak bone mass obtained by age 30 years, and on the other side is the ongoing bone loss because of aging and the estrogen deprivation of menopause. Each individual has their unique "osteoporosis equation" based primarily on genetics and several modifiable risk factors (Table 2). One of the most influential risk factors is a parent who suffered a nontraumatic fracture.[23] Two hundred to more than 500 loci associate with bone mineral density (BMD) and fractures.[24,25] Also, single nucleotide polymorphisms associate with AI-induced bone loss or fractures.[26,27] Thus osteoporosis is a complex genetic disease with several modifiable risk factors.

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Table 1 Comparison of ZA and DEN.

Factor	ZA (iv)	DEN (sc)
Dose	5[b] or 4 mg[a]	60[a] or 120 mg[c]
Mechanism	Osteoclast inhibitor	RANKL monoclonal antibody
Metabolism	Not metabolized	Not metabolized
Half-life	2.5 hrs,[d] 188 days[e]	28 days
Clearance	Renal	RES
Schedule		
Skeletal metastases	Every 3 months	Monthly
Osteoporosis	Every 6 months	Every 6 months
Common side effects	Fever, chills, anemia, dyspnea, constipation, muscle, bone or joint pain, nausea, fatigue, and vomiting	Joint, muscle pains; fatigue, and hypocalcemia
Rare side effects	Osteonecrosis; renal insufficiency[f]; atypical femur fractures[164]	Osteonecrosis; rebound vertebral fractures[138] and atypical femur fractures[165]
Dose modifications	For creatine clearance < 60 mL/min modify ZA as follows:	None
	50-60 min/mL = 3.5 mg	
	40-49 min/mL = 3.3 mg	
	30-39 min/mL = 3.0 mg	
	Do not give ZA when the creatinine clearance < 30 mL/min	
Costs[g] (US dollars)	252.00	1906.00

Abbreviations: DEN = denosumab; iv = intravenous; RES = reticuloendothelial system; sc = subcutaneous; ZA = zoledronic acid.
[a] Once every 6 months (usual dose for osteoporosis prevention or treatment of women with early-stage breast cancer).
[b] One dose annually (US Food and Drug Administration–approved osteoporosis dose in non-cancer individuals).
[c] The dose for skeletal metastases.
[d] The half-life in blood.
[e] Most goes to bone.
[f] Dose-dependent and rate of infusion dependent.
[g] Costs of drug and administration from the Centers for Medicare and Medicaid Services Reimbursement (www.cms.gov).

Table 2 Risk Factors for Osteoporosis.

Risk Factor in General Population	With BMD RR	95% CI	Ref
Parental history of nontraumatic fracture	2.11	1.41-3.14	28
Ever use of steroids[a]	2.25	1.60-3.15	29
Rheumatoid arthritis	1.73	0.94-2.30	30
Alcohol intake of more than 2 to 3 drinks/day	1.70	1.20-2.42	31
Prior nontraumatic fracture after age 50 years[a]	1.62	1.30-2.01	32
Current smoking	1.60	1.27-2.02	33
Low body mass index[a]	1.42	1.23-1.65	34
Risk factors for fractures in women with early-stage breast cancer			
Hypogonadism (CIOF or GnRH agonist +/- AI)	NA		
Oophorectomy	1.54[b]	1.29-1.82	35
AI	1.55[c,d]	1.31-1.83	36

Abbreviations: AI = aromatase inhibitor; BMD = bone mineral density; CI = confidence interval; CIOF = chemotherapy-induced ovarian failure; GnRH = gonadotrophin-releasing hormone; NA = not available; RR = relative risk.
[a] Risk factor in men.
[b] Standardized incidence ratio in elderly women without breast cancer.
[c] Relative to tamoxifen.
[d] Hazard ratio.

Risk Factor Assessment and Screening for Osteoporosis

Table 2 describes the risk factors for osteoporosis.[28-36] Genetic factors include low body mass index, personal or parental history of nontraumatic fracture, and rheumatoid arthritis. Lifestyle interventions include smoking cessation, decreasing alcohol consumption, and increasing physical activity. These lifestyle modifications also promote overall health. Oophorectomy, AIs with or without GnRH agonists, and CIOF are also risk factors for bone loss. Exercise does not lower the fracture risk in the general popula-

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Figure 2 The 10-year hip fracture risk by T-score and age in the general population. The fracture risk increases by age and T-score. For example, a 70-year-old person with a T-score of –3.0 has a hip fracture risk of approximately 13% over the next 5-years.

tion and postmenopausal women with breast cancer,[37,38] whereas premenopausal women who exercised lessened bone loss in the femoral neck but did not affect the lumbar spine.

The best screening test for osteoporosis is dual-energy x-ray absorptiometry (DXA) scanning of the lumbar spine, hip, and femoral neck. The T-score is the critical variable of DXA, correlating with fracture risk.[39] Figure 2 describes the risks of fractures by age and T-scores. The T-score is the number of standard deviations (SDs) above or below that of a reference population of women aged 20 to 29 years. Normal BMD is a T-score of –1 or above, osteopenia is –1 to –2.5, and osteoporosis –2.5 or below or experiencing a nontraumatic fragility fracture.[40] For every 1 SD decrease in T-score, the fracture risk increases 1.5- to 2.5-fold. The Z-score represents the number of SDs above or below that of an age-matched reference population. The Z-score is useful for assessing potential causes of secondary osteoporosis.

The trabecular bone score (TBS) is a newer method of assessing bone microarchitecture derived from DXA scan.[41] The TBS adds to DXA and Fracture Risk Assessment Tool (FRAX) score in predicting fracture risk in aromatase-treated women.[41] Although TBS is promising, it is as yet not part of standard screening practice.

The Magnitude of Bone Loss Related to Breast Cancer Treatments

Healthy postmenopausal bone loss is approximately 1 to 2 percentage (%) change per year.[42] AIs alone lose 2% to 3% bone per year.[43] In premenopausal women, bone loss is approximately 7% per year for CIOF[44] and 7.7% per year for GnRH agonists, respectively. Using GnRH agonists, combined with AI, the bone loss is approximately 11% per year (data not shown).[45] Premenopausal women (without risk factors or secondary osteoporosis) often do not need osteoporosis treatment because they are closer in age to their peak bone mass.

Aromatase Inhibitors

AIs (ie, anastrozole, letrozole, and exemestane) are used only in postmenopausal women (ie, natural menopause defined as absence of menses for 12 months, bilateral oophorectomy, or GnRH agonists with estradiol suppressed) are superior to tamoxifen in randomized trials and a meta-analysis in which statistically significant improvements in disease-free, bone metastasis-free, and overall survival were noted.[46,47] AIs are specific enzyme inhibitors of the P450 cytochrome aromatase (or CYP19).[48] Aromatase is responsible for converting androgens to estrogens in postmenopausal women and is in many tissues, including adipose, ovary, breast, bone, and brain. Functionally, AIs serve to lower estrogen levels in postmenopausal women. The major trials of AIs are described in Table 3.

Table 3 illustrates the fracture risks of AIs versus tamoxifen.[49-53] Women treated with AIs have statistically significantly higher rates of fractures than tamoxifen.[54] The fracture remains elevated during the 5-year treatment period, and during years 5 to 10, the fracture rates decrease to the level of tamoxifen fracture rates.

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Figure 3 Algorithm for bone heath in women with breast cancer. Assessment of fracture risk starts with dividing the risk factor assessment into modifiable and non-modifiable risks. Every woman should take 800 to 1000 IU/day of vitamin D3 and calcium 1200 mg/day (made up of dietary sources and supplemental calcium). Vitamin 25-OH deficiency (20 ng/mL or less) or insufficiency (30 ng/mL) is common in the general population and breast cancer survivors and should be corrected. Obtain a DXA scan; if T-score is –1.5 or greater in the femoral neck, repeat DXA every 2 years. Institute treatment with an oral bisphosphonate, ZA or DEN if the T-score is less than –1.5 with 2 or more risk factors (ie, receiving treatment with an AI, GnRH agonist, CIOF, age over 65 years, family history of hip fracture, body mass index of less than 20, fragility fracture at age less than 50 years, or current smoking), the FRAX score shows that major osteoporotic fracture, or the hip fracture risk is 3% or more, or the T-score is lower than –2.5 or an osteoporotic fracture. Repeat DXA every 2 years. Abbreviations: AI = aromatase inhibitors; CIOF = chemotherapy-induced ovarian failure; DEN = denosumab; DXA = dual-energy x-ray absorptiometry; FRAX = Fracture Risk Assessment Tool; GnRH = gonadotrophin-releasing hormone agonist; IV = intravenous; sc = subcutaneous; ZA = zoledronic acid.

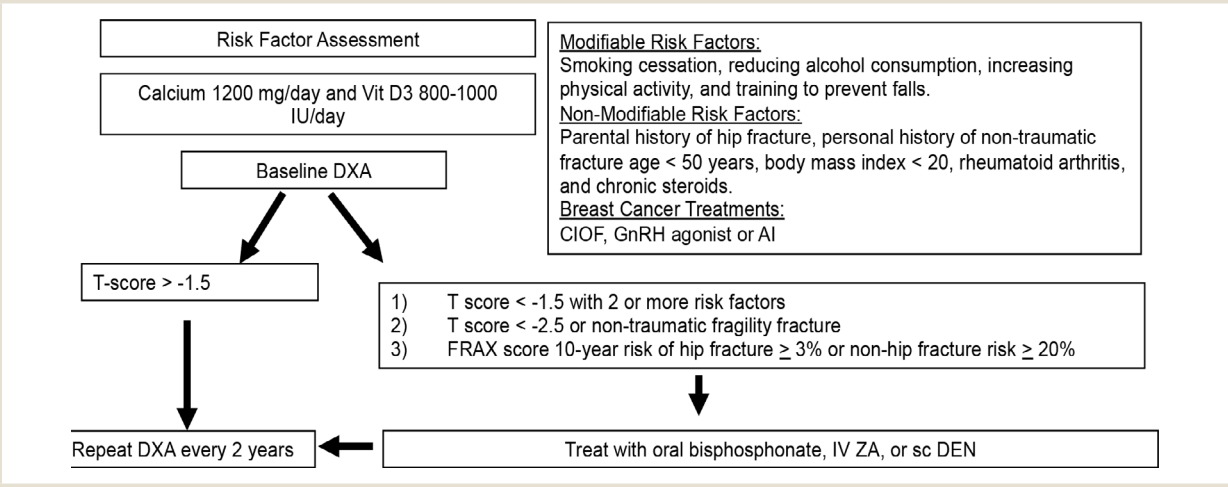

Table 3 Fractures Rates in Randomized Trials of Aromatase Inhibitors Versus Tamoxifen.

Trial	N	Follow-Up (mo.)	Treatment	Fractures (%)	*P* Value	Ref
AI vs. TAM						
ATAC	9336	100	ANA vs. TAM	11 vs. 7.7	< .001	49
BIG 1-98	4922	60	LET vs. TAM	9.3 vs. 6.5	.002	50
AI after 2 to 3 years of TAM						
TEAM	9779	61	EXE vs. TAM	5.0 vs. 3.0	.0001	51
ABCSG8/ARNO	3224	28	ANA vs. TAM	2.0 vs. 1.0	.015	52
AI after 5 years of TAM						
MA-17	5187	63	LET vs. TAM	5.2 vs. 3.1	.02	53

Abbreviations: ABCSG8 = Austrian Breast Cancer Study Group trial 8; AI = aromatase inhibitor; ANA = anastrozole; ARNO = Anastrozole-Noveldex trial 95; ATAC = Anastrozole, Tamoxifen Alone or in Combination; BIG = Breast International Group trial 1-98; TEAM = Tamoxifen, Exemestane Adjuvant Trial; EXE = exemestane; LET = letrozole; MA-17 = ; National Cancer Institute of Canada Clinical Trials Group trial MA-17; TAM = tamoxifen.

Selective ER Modulators

Tamoxifen is effective as an anticancer drug in pre- and postmenopausal women. Tamoxifen binds to the ER and, depending on tissue specificity, acts as an estrogen agonist or antagonist. In postmenopausal women, tamoxifen mitigates bone loss acting as an agonist, whereas in premenopausal women it acts as an antagonist and causes loss of bone.[55,56] The results from a randomized double-blind P1 study of tamoxifen versus placebo shows that the number of hip, spine, and Colles fractures were numerically smaller, although not statistically significantly so in tamoxifen-treated versus placebo women over age 50 years, but not in women younger than age 49.[57] Another selective ER modulator, raloxifene, is US Food and Drug Administration (FDA)-approved for osteoporosis and breast cancer prevention in high-risk women. The results of the randomized P2 trial comparing tamoxifen to raloxifene show no differences in any sites of fracture.[58] Raloxifene should not be used when treating breast cancers because the only data are in the prevention setting.

CIOF, Oophorectomy, and GnRH agonist +/- AI

The mechanism of CIOF is gonadal cytotoxicity occurring with age-related decreases in ovarian reserve related to a reduction in the number and quality of ovarian follicles.[59] CIOF is related to increasing age (ie, older premenopausal women are more likely to develop

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CIOF than younger women). Also, CIOF is drug-specific (ie, alkylators, such as cyclophosphamide, followed by platinum, anthracyclines, and taxanes) and related to the cumulative dose and duration of treatment.[60] It is important to remember that transient amenorrhea may occur after chemotherapy.[44,61] Only approximately 10% of women over age 40 years will have menstrual function returns, whereas up to 50% of those younger than 40 years will have menstrual function returns. Women with amenorrhea should use contraception as they can still ovulate. After chemotherapy, women who retain menstrual function may go to menopause at earlier ages than women who did not receive chemotherapy.[62] Both will influence antiestrogen treatment choices in women with ER-positive breast cancers. Oophorectomy or GnRH agonist with or without AI increases the risks of bone loss and fractures.[63]

Calcium and Vitamin D

In a high-quality metanalysis with a low risk of biases, supplemental calcium was not effective in reducing fractures at any site.[64] Vitamin D alone does not decrease fractures.[65] Supplemental calcium and vitamin D lead to a slight decrease in the risk of hip fractures, but not spinal fractures, in institutionalized individuals at high risk of osteoporosis. However, supplemental calcium and vitamin D decrease postmenopausal bone loss[40] and reduce falls,[66,67] hence reduces fractures in an aging population.

Vitamin D deficiency (< 20 ng/mL of 25-OH vitamin D) and insufficiency (between 20 and 30 ng/mL of 25-OH vitamin D) are prevalent in the general population and women with breast cancer, especially in minority populations.[68-70] Before initiating AIs or when the first DXA scan shows osteopenia, check a 25-OH vitamin D level. Trials of supplemental calcium and vitamin D in cancer treatment-induced bone loss or women receiving AIs are few in number. These trials show no effect mitigation of BMD.[71] There is consensus among policy-making organizations (eg, National Osteoporosis Foundation [VA, USA], the US Preventative Services Task Force [MD, USA], the National Academy of Sciences, and the Institute of Medicine [both in Washington DC]) that women over the age of 50 years should receive 1000 to 1200 mg of calcium (including dietary and supplemental) and 800 to 1000 IU of vitamin D3 (cholecalciferol) per day.[40] Several position papers and reviews recommend the same doses for women receiving AIs.[72-74]

Determining Fracture Risk

One of the strongest risk factors for AI-induced fractures is having osteopenia or osteoporosis when starting AIs.[75] Validated tools to assess fracture risk in non-cancer generally are the FRAX, Garvan, and others.[76,77] The development of FRAX (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9) uses clinical risk factors (ie, age, height, weight, sex, prior personal history of fracture, parental history of hip fracture, current smoking, glucocorticoids, secondary osteoporosis, alcohol greater than 3 drinks/day) with or without femoral neck BMD to estimate the 10-year risk of a hip or non-hip fracture.[78] There are versions of FRAX specific for each country. A 10-year risk of hip or non-hip fracture that exceeds 3% or 20% indicates treatment with antiresorption drugs. The Garvan calculator (https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/) uses age, sex, prior history of fracture, prior history of falls, and BMD measurement. It also provides 5- and 10-year risk of hip and non-hip fragility fracture. Indicated are antiresorptive therapies if the 10-year risks are 3% to 9% and 14% to 26% for hip and non-hip fractures, respectively.

Modifications to FRAX when assessing AI-induced bone loss include checking "secondary osteoporosis."[42] This practice is called into question by a Canadian-based registry cohort study. In the registry study, the designation of "secondary osteoporosis" as a risk factor for AI-induced bone loss overestimated the fracture risk.[79] In the same Canadian registry, women initiating AI-therapy had higher body mass index, higher BMD, lower osteoporosis prevalence, and fewer prior fractures than women not starting AIs or the healthy population.[80] The implications being that AIs do not cause as many fractures as previously thought. These 2 studies are case-control registry studies and, as such, subject to several biases.[81]

Assessing the Need for Antiosteoporosis Therapy in Early-Stage Disease

Various policy-making organizations have guidelines for preventing or treating osteoporosis in cancer survivors[42,82] or AI-induced bone loss.[83] All guidelines begin with risk factor assessment (Table 2), making lifestyle changes that promote bone health and overall health, including smoking cessation, reducing alcohol consumption, increasing physical activity, and taking adequate amounts of daily calcium of vitamin D3. The screening, prevention, and treatment of osteoporosis in cancer are similar to non-cancer populations.[77] The significant difference is that some breast cancer treatments cause bone loss,[84] which in some women increases the risk of osteoporosis. A suggested algorithm for bone is suggested in Figure 4 (derived from references [39] and [80]).

Trials of women with breast cancer use BMD as a surrogate for fractures (Table 4).[85-89] The exception is the Austrian Breast Cancer Study Group (ABSCG) trial 18, whose primary endpoint was fracture reduction. ABCSG trial 18 is a randomized, double-blind, placebo-controlled trial of DEN or placebo in 3425 postmenopausal women receiving AI.[90] With a median follow-up of 6 years, the fracture hazard rate (HR) was 0.50 (95% confidence interval [CI], 0.39-0.65). In an update of the AZURE trial[91] with 7 years of follow-up, the 5-year rate of fracture was 3.8% (95% CI, 2.9%-4.7%) for the ZA group and 5.9% (95% CI, 4.8%-7.1%) in the controls. Comparative efficacy analyses for antiosteoporosis drugs show oral bisphosphonates, ZA, and DEN all reduce fractures.[92,93]

Teriparatide is FDA-approved for use in osteoporosis (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021318s053lbl.pdf). This drug is part of human PTH and stimulates osteoblasts to form new bone. There is contraindication for osteosarcoma. Although not formally contraindicated in women with breast cancer, PTH receptors and PTH-related protein are expressed in breast cancers. This has led to a common sense approach to avoid teriparatide in women diagnosed with breast cancer.

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Figure 4 Schematic representation of when cancers go to bone. (1) Vicious cycle; (2) RANKL expressed by osteocytes and cancer cells increases the recruitment of monocytes and stimulates osteoclast differentiation; (3) osteocytes increase the release of SOST (sclerostin) and DKK1 that inhibit osteoblasts and increase the expression of RANKL; (4) notch signaling pathway activation increase osteocyte apoptosis and increases proliferation of cancer cells; (5) osteocyte apoptosis signals promote osteoclastic activity; (6) adenosine triphosphate (ATP) is hydrolyzed to adenosine by the activity of enzyme complex CD39/CD73, and adenosine binds to the adenosine receptor in cancer cells increasing proliferation, migration, and metastases; (7) extracellular adenosine increases osteoclast activity; and (8) promotes Treg activity, and increases immune tolerance. Used with permission from Riquelme MA, Cardenas ER, Jiang JX. Osteocytes and bone metastasis. Front Endocrinol (Lausanne) 2020; 11:567844.

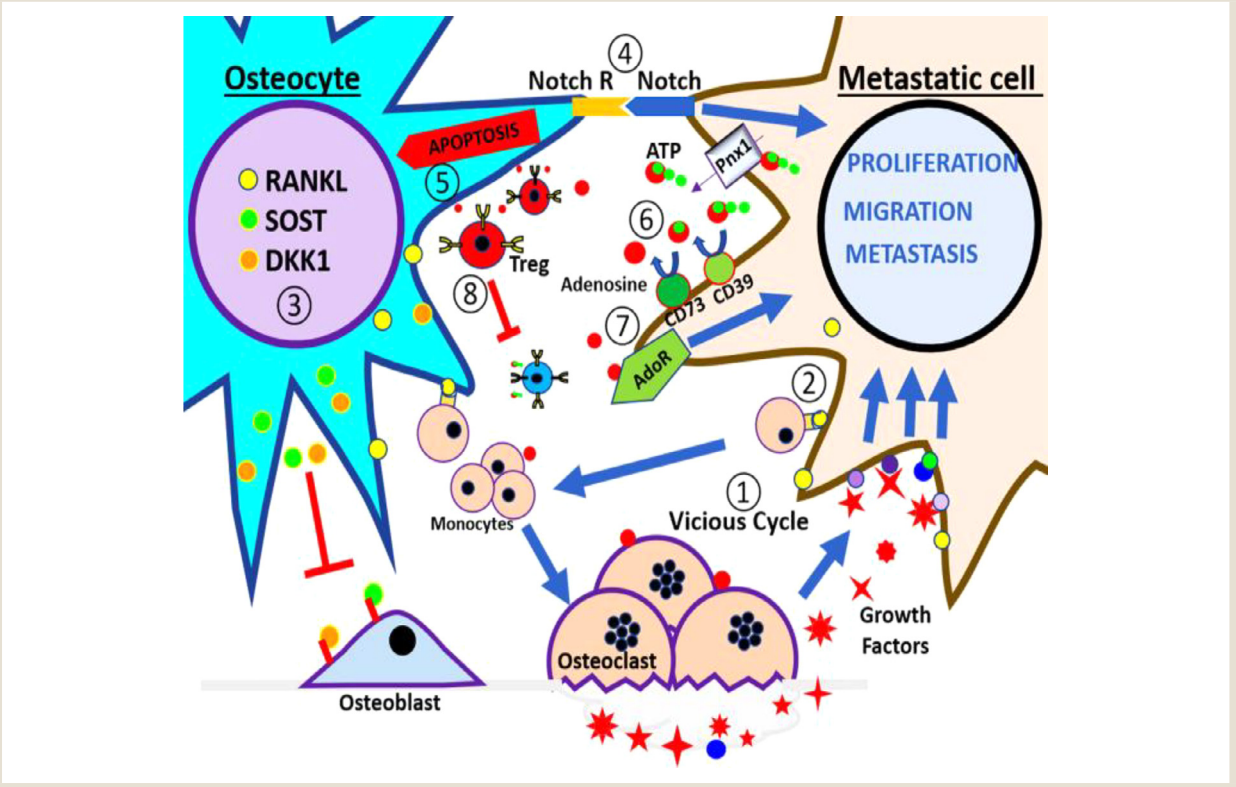

Table 4 Major Randomized Trials for Bone Loss in Early-Stage Breast Cancer.

Trial	Treatments	*n*	Results (L/S BMD)[a]	*P* Value	Ref
CIOF					
Hershman	ZA 4 mg q3 mo for 1 yr vs. placebo	101	0 vs. −3.0	< .001	85
Shapiro	ZA 4 mg q3 mo for 1 yr vs. control	441	1.2 vs. −6.7	< .001	86
Gnant	ZA 4 mg q6 mo for 3 yrs vs. control[b]	401	4.0 vs. −6.7	.02	87
AI					
Brufsky	ZA 4 mg IV q6 mo for 1 yr vs. delayed	502	2.0 vs. −2.5	< .001	88
Coleman	ZA 4 mg IV q6 mo for 5 yrs vs. delayed	1065	4.3 vs. −5.4	< .0001	89
Ellis	DEN 60 mg sc q6 mo for 2 yrs vs. placebo	262	6.0 vs. −1.6	< .0001	166
Gnant	DEN 60 mg sc q6 mo for 5 yrs vs. placebo	3425	HR fractures = 0.50 95% CI 0.39-0.65	< .0001	90
Van Poznak	Risedronate oral 35 mg/week for 2 yrs vs. placebo	111	2.2 vs. −1.85	< .0001	167

Abbreviations: AI = aromatase inhibitor; BMD = bone mineral density; CI = confidence interval; CIOF = chemotherapy-induced ovarian failure; DEN = denosumab; GnRH = gonadotrophin-releasing hormone; HR = hazard ratio; iv = intravenous; L/S = lumbar sacral spine; sc = subcutaneous; TAM = tamoxifen; ZA = zoledronic acid.
[a] Percentage change in the lumbar spine.
[b] GnRH agonist + TAM or AI.

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Tumors Metastasizing to Bone and Pathophysiology of Skeletal Metastases

The metastatic process of the bone is complex and is the subject of several recent reviews.[94-98] Originally known as the "vicious cycle,"(Figure 4)[97-100] metastases secrete cytokines, including transforming growth factor-alpha, IL-8, and vascular endothelial growth factor that stimulate osteoclasts to resorb bone and inhibit osteoblast activity. In turn, osteoclasts secrete insulin-derived growth factor, transforming growth factor-beta and others that promote bone metastases growth. The osteocyte has a major role in skeletal metastases described in Figure 4. [101]

Before the vicious cycle is established, breast cancer cells must enter the bone in a multistep process that begins with breast cancer cells escaping from the primary tumor, cancer cells intravasation into the blood vessels, homing to the bone, adhering, and invading into bone (see Wang et al., for a thorough discussion of this topic).[94,102,103] After breast cells invade into the bone, these cells then may go into a period of dormancy or quiescence,[97,104] in which they may manifest years to decades later as bone metastases.[105] In particular, dormancy is characteristic of luminal A cancers, in which approximately one-half of the distant recurrences occur after 5 or more years.[106]

Many cells beyond osteoclasts and osteoblasts are involved in the bone marrow metastatic niche, including osteocytes,[107] mesenchymal stem cells, adipocytes, hematopoietic stem cells, macrophages, lymphoid cells, endothelial cells, and nerves cells.[108] Also, there are many cytokines, microRNAs,[109,110] and other factors involved in the dysregulation of osteoclasts or osteoblasts when breast cancer goes to the bone.[110,111]

Approximately one-third of breast cancer metastases are predominantly lytic, one-third mixed lytic and sclerotic, and one-third predominately sclerotic. Lytic lesions reflect osteoclastic overactivity, whereas sclerotic bone metastases result from overactivity of osteoblasts.[94] Critical factors in sclerotic metastases (this information is based primarily on preclinical experiments using prostate cancer cell lines) include osteoblastic activation by cancer cell-derived parathyroid-hormone-related protein, IL-1, IL-8, endothelial-1 (ET1), and Dickkopf-1. ET1 stimulates osteoblasts via endothelin A receptor that actives Wnt signaling in osteoblasts.[112] Wnt signaling is critical for stimulating osteoblast differentiation and activation.[113] in advanced disease.

Clinical Trials of Bone-Modifying Agents in Skeletal Metastases

In breast cancer, metastases to the skeleton are the most common initial site affecting 50% to 70% of women.[114] Standard practice includes oral N-amino bisphosphonates, ZA, and the RANK ligand inhibitor, DEN, in the United States. Some earlier trials used the less potent oral bisphosphates clodronate (not approved in the United States) and ibandronate (IBD; not approved in the United States for treatment of skeletal metastases). ZA and reduce the incidence of skeletal-related events (SRE), including pathological fracture, spinal cord compression, radiation, or surgery to bone. Table 5 describes the major randomized trials of bone-modifying agents (BMA) in skeletal metastases.[115-125] IBD was inferior to ZA with annual rate SRE of 0.499 (95% CI, 0.454-0.549) and 0.435 (95% CI, 0.393-0.480), respectively, HR = 1.148 (95% CI, 0.967-1.362)[117]

The largest trial involving over 2000 women with breast cancer with skeletal metastases compared monthly ZA 4 mg intravenous (IV) versus DEN 120 mg subcutaneously (sc).[122] The primary endpoint was time to first SRE, and the secondary endpoint was time to first and subsequent SREs. The skeletal morbidity rate (the number of SREs per patient divided by the patient's time at risk) was 0.45 and 0.58 events per patient per year (P= .004) for the DEN and ZA, respectively. DEN delayed the time to first SRE by 18% (HR = 0.82; 95% CI, 0.71-0.95; P= .01), and the time to first and subsequent SREs by 23% (HR = 0.77; 95% CI, 0.66-0.89; P= .001). Importantly, there were no difference in disease progression (HR = 1.0; 95% CI, 0.89-1.11; P= .93) or overall survival (HR 0.95; 95% CI, 0.81-1.11; P= .49). Also, severe, grade 3, or higher toxicity was similar between the 2 groups. Despite the significant delay in SRE in favor of DEN, the joint American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) concluded there was insufficient evidence to choose one BMA over the other.[126]

Three randomized trials established the noninferiority of every 3-month ZA versus monthly ZA.[123-125] The largest of these was the Cancer and Leukemia Group B trial 70604 that randomized 1822 individuals (855 breast cancer; 689 prostate cancer; 278 multiple myelomas) to either ZA monthly or ZA every 3 months.[123] In the intent-to-treat breast cancer analysis, the proportion of women experiencing at least one SRE was not different (P= .50). There was no significant difference in osteonecrosis rates in the 4-week versus every 3 months (2% vs. 1%, adjusted for baseline serum creatinine, prior SRE, and prior use of oral bisphosphonates; P= .08). However, there was an increase in the creatinine level (adjusted for baseline serum creatinine, prior SRE, and prior use of oral bisphosphonates; P= .02) for every 4-week treatment arm. In the other 2 randomized trials for the first year, women received every 4-week ZA. In the second year, there was randomization to every 4 weeks versus every 3 months, both trials demonstrating noninferiority.[124,125] In the ASCO and CCO guidelines, their conclusion was every 4-week and every 3-month ZA were acceptable options.[126]

Cost-Effectiveness

Several cost-effectiveness (CE) analyses compare monthly ZA to monthly DEN,[127-132] and 1 compares every 3-month ZA to monthly DEN.[10] Novartis (makers of ZA) or Amgen (denosumab) sponsored several of these CE analyses. The outcome of Pharma-sponsored CE analyses reflected the drug manufacturers (ie, Novartis-sponsored CEs concluded that ZA was CE relative to DEN, and vice versa). There were 2 non-Pharma CE analyses. The cost differential between generic ZA and proprietary DEN is that every 3-month ZA is CE relative to monthly DEN.[10] In a systemic review that included individuals with breast and prostate cancer, ZA was CE relative to DEN.[128]

Adverse Events

Fever, chills, muscle, bone or joint pain, nausea, fatigue, and headaches are common side-effects related to ZA (Table 3), whereas joint, muscle pains, and asymptomatic hypocalcemia are side-effects related to DEN. The side-effects of ZA and DEN are self-limited.

Please cite this article as: Charles L. Shapiro, Bone-modifying Agents (BMAs) in Breast Cancer, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2021.04.009

Table 5 Major Randomized Trials of Bone Modifying Agents in Skeletal Metastases.

Trial	Therapy	*n*	Primary Endpoint	Results	Ref
Oral bisphosphonates					
Body	IBR vs. placebo	564	SMPR	0.95 vs. 1.18 ($P = .004$)	115
Barrett-Lee	IBR vs. ZA	705	SRE	HR = 1.48 (95% CI, 0.97-1.36)[a]	117
Paterson	CLO vs. placebo	173	CRSE	219 vs. 305 per 100 patient-years ($P < .001$)	116
ZA					
Rosen	ZA vs. PAM	1648	SMR	1 vs. 1.39 ($P = .084$)	119
Lipton	ZA vs. PAM	442	SRE	33% vs. 44% ($P = .021$)	120
Rosen	ZA vs. placebo	507	SRE	39% vs. 48% ($P = .039$)	118
DEN					
Lipton	DEN vs. ZA	255	SRE	12% vs. 16%	121
Stopeck	DEN vs. ZA	2049	Time to first SRE Time to first and subsequent SRE	HR = 0.82 (95% CI, 0.71-0.95; P = .01) HR = 0.77 (95% CI, 0.66-0.89; $P = .001$)	122
Schedule					
Himelstein	Mo. ZA vs. every 3 mo. ZA	855	SRE	27% vs. 29% ($P = .001$ for noninferiority	123
Hortobyagi	Mo. ZA vs. every 3 mo. ZA	416	SRE	22% vs. 23% ($P = .02$ for noninferiority)	124
Amadori	Mo. ZA vs. every 3 mo. ZA	425	SMR	0.22 vs. 0.26 (The between-group difference was 0.04 and the upper limit of one-tailed 97.5% CI was 0.17, which is lower than the non-inferiority margin.)	125

Abbreviations: CLO = clodronate; CSRE = combined skeletal morbidity rate; DEN = denosumab; HR = hazard ratio; IBR = ibandronate; mo. = month; PAM = pamidronate; SMPR = skeletal morbidity period rate; SMR = skeletal morbidity rate; SRE = skeletal-related event; ZA = zoledronic acid.

The ZA renal dysfunction is related to the rate of infusion, dose, and duration of treatment. Oral bisphosphonates primarily have gastrointestinal side effects. In particular, oral bisphosphonates have compliance concerns.

ZA and DEN both cause the side effect of medication-related osteonecrosis of the jaw (MRONJ).[133] The incidence of MRONJ is duration-dependent with significantly higher rates 2 years and beyond. In a large prospective cohort study, the cumulative incidence of ZA-related MRONJ in 1120 women with breast cancer and skeletal metastases was 0.3% (95% CI, 0.1%-0.8%), 1.4% (95% CI, 0.8%-2.3%), and 2.4% (95% CI, 1.5%-3.4%) for 1, 2, and 3 years, respectively.[134] The optimal duration of bisphosphonates is uncertain. Limited to 2 years of BMA, as is common practice, the incidence of MRONJ is between 1% and 2% for both ZA and DEN.[135] The incidence of MRONJ with oral bisphosphonates is less than that with IV ZA. Pretreatment, a dental screening examination is necessary as dental work (ie, extractions, alveoloplasties, or implants) during treatment with BMA increases the risk of MRONJ.[133] Avoid elective dental (eg, extractions, alveoloplasties, or implants) procedures during treatment with BMA. Women should be encouraged to maintain routine dental care and cleanings during treatment with BMA.

An atypical femur fracture is a rare side effect after prolonged treatment with ZA, DEN, or oral bisphosphonates.[136] The incidence varies widely in cancer populations because of the paucity of data. In a systemic review in non-cancer populations, the overall incidence was rare, estimated as 3.0 to 9.8 per 100,000 patient-years.[137] Multiple rebound vertebral fractures (MRVF) infrequently occur after discontinuation of DEN. One of the best data sources about MRVF is from the Freedom Trail in postmenopausal osteo-

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porosis treated with DEN or placebo.[138] The incidence of MRVF was 3.4 per 100 person-years for the DEN group and 2.2 per 1000 patient-years for the placebo group. In response to MRVF, some have advocated the ZA after discontinuation of DEN.[82]

Antiosteoporosis Drugs and their Anticancer Activity

Disseminated tumor cells (DTCs) reside in the bone marrow and contribute to metastases at other sites.[108] DTCs serve as a prognostic factor in early breast cancer,[139] and ZA can reduce DTCs in the human bone marrow.[140,141] Observations in preclinical models of bisphosphonates and DEN show anticancer effects.[142,143] These observations provide a testable hypothesis in the clinic: antiosteoporotic drugs not only mitigate bone loss and reduce fractures but have anticancer effects as well.

Several randomized trials[90,144-147] and meta-analysis restricted to the bisphosphonates[148] show statistically significant reductions in skeletal metastases and cancer mortality but only in postmenopausal women or premenopausal women rendered postmenopausal by a GnRH agonist. The Early Breast Cancer Trialists' Collaborative Group (EBCTGC) included over 6000 premenopausal and over 11,000 postmenopausal women. Although there was no effect in premenopausal women, there was an absolute reduction in bone metastases (2.2%, $P = .0002$) and cancer mortality (3.3%, $P = .002$) in postmenopausal women. Additional trials are needed to confirm the results of the meta-analysis.[149]

In 2017, the Joint Canadian Care Ontario and American Society of Clinical Oncology Practice Guideline, and the National Network of Comprehensive Cancer Centers put out a statement saying to "consider" ZA (4 mg IV) every 6 months for 3 to 5 years, or oral clodronate (1600 orally/day, not available in the United States) for 3 years in high-risk postmenopausal women.[150,151] At St. Gallen/Vienna Consensus Discussion, 53% of consensus participants said "yes," but 37% of them said "no" to the use of adjuvant ZA with ovarian suppression and AI or tamoxifen[152] Finally, the European Society of Medical Oncology recommends adjuvant bisphosphonates for those who undergo ovarian suppression or who are postmenopausal, especially if they are at a high risk of relapse.[153] Thus there is still considerable uncertainty about the use of adjuvant ZA.

Two trials of DEN are published. The randomized, placebo-controlled D-CARE of adjuvant DEN versus placebo,[154] and the Austrian Breast Cancer Study Group (ABCSG) trial 18 was another randomized placebo-controlled trial whose primary endpoint was fractures.[90] In D-CARE (n = 4509), the DEN schedule was intensive with sc every 3 to 4 weeks for the first 6 months, then every 3 months for 5 years. The D-CARE trial was a wholly negative trial in postmenopausal women with no reductions in breast cancer mortality and bone-metastases for the DEN versus placebo-treated women.

ABCSG trial 18 (n = 3425) with 6 years of median follow-up, the disease-free survival was statistically significantly higher in favor of the DEN treatment (hazard ratio [HR] = 0.82; 95% CI, 0.69-0.98; $P = .026$).[155] However, when one looks at hard endpoints (eg, invasive local-regional and distant recurrences, invasive contralateral breast cancers, and deaths), there were no differences between DEN and placebo. Contributing to "statistical significance" was non-histologically verified distant metastases and second breast cancers and non-breast invasive cancers. There is no evidence thus far to use DEN as an anticancer drug.

Future Directions

Romosozumab is a monoclonal antibody that inhibits sclerostin, and the FDA approved it in 2019 for postmenopausal osteoporosis.[156,157] Sclerostin is a soluble Wnt inhibitor that represses osteoblast differentiation. In preclinical studies, antisclerostin antibody reduced bone metastases, stimulated osteoblastic-mediated new bone formation, and reduced osteoclast-mediated bone resorption.[158] Trials of romosozumab in skeletal metastases and for individuals with early cancers for treatment-related osteoporosis are warranted. Identifying a new RANKL receptor, the leucine-rich repeat-containing G protein-coupled receptor represents a new target.[159] Oral RANKL inhibitors[160] and aptamers, single-stranded oligonucleotides that target RANKL, are in development.[161]

Conclusion

BMAs prevent or treat osteoporosis and reduce the complications of skeletal metastases. Nontraumatic fractures are sources of morbidity and mortality and are preventable.[162] Dissimilar to other chronic diseases, the first symptom of osteoporosis may be a fracture, emphasizing the importance of screening, prevention, and treatment of osteoporosis in women with breast cancer. Some data support the use of ZA as an anticancer drug. Despite guidelines,[42] and algorithms,[72] compliance with recommendations is often lacking.[163] Lifestyle interventions that promote bone health also promote overall health and are the first-line approach to bone loss.

Also, BMAs are standard in the treatment of skeletal metastases. ZA and DEN reduce SREs but do not improve progression-free or overall survival. Based on noninferiority randomized trials, dose de-escalation of monthly ZA to every 3-month ZA is an accepted alternative to monthly dosing. Similar dose de-escalation trials are ongoing for DEN. ZA and DEN both have a 1% to 2% risk of MRONJ, and it is important to obtain a dental screening examination pretreatment with these drugs. The ZA anticancer activity is controversial, and policy-making organizations in the United States conclude to "consider" the use of ZA in "high-risk" postmenopausal or premenopausal women receiving GnRH agonists. There are insufficient data to use DEN as an anticancer drug at this time.

Disclosure

No.

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Please cite this article as: Charles L. Shapiro, Bone-modifying Agents (BMAs) in Breast Cancer, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2021.04.009

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Please cite this article as: Charles L. Shapiro, Bone-modifying Agents (BMAs) in Breast Cancer, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2021.04.009

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Please cite this article as: Charles L. Shapiro, Bone-modifying Agents (BMAs) in Breast Cancer, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2021.04.009

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Please cite this article as: Charles L. Shapiro, Bone-modifying Agents (BMAs) in Breast Cancer, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2021.04.009