

EDITORIAL

Managing bone mineral density with oral bisphosphonate therapy in women with breast cancer receiving adjuvant aromatase inhibition

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See related research by Markopoulos *et al.*, <http://breast-cancer-research.com/content/12/2/R24>

Abstract

The use of adjuvant aromatase inhibitors is associated with an increased risk of osteoporosis and fractures. The oral bisphosphonate, risedronate – dosed as the US Food and Drug Administration approved for the treatment or prevention of postmenopausal osteoporosis – appears to mitigate bone loss associated with 2 years of adjuvant anastrozole in women with early-stage breast cancer.

The estrogen deprivation associated with the adjuvant aromatase inhibitors (AIs) has been shown to increase the risk of bone loss and fragility fractures. Minimizing treatment toxicities and preserving bone health are important aspects of adjuvant breast cancer care.

Markopoulos and colleagues performed a phase III multicenter clinical trial investigating the affect of the oral bisphosphonate, risedronate, on bone mineral density (BMD) changes in postmenopausal women with hormone receptor (HR)-positive early-stage breast cancer receiving adjuvant anastrozole [1]. This study – given the moniker ARBI – enrolled women with HR-positive early-stage breast cancer scheduled to receive adjuvant anastrozole 1 mg daily, and the study participants were stratified into three categories based on their baseline BMD. Those with BMD of at least -1.0 (low risk for fracture) were treated with anastrozole without bisphosphonate therapy. Those with BMD of at least -2.0 were treated with anastrozole plus risedronate 35 mg weekly (higher risk for fracture). The women to receive anastrozole with BMD less than -1.0 but greater than -2.0 were considered at intermediate

risk for fracture and were randomized to either risedronate 35 mg weekly or control. All patients received calcium and vitamin D supplementation.

The study design of the ARBI study, like those of the ARIBON [2] and SABRE [3] trials, is extremely practical. The study participants are postmenopausal women and the drug, dose and schedule of the study intervention are couched in the literature for managing bone mass in postmenopausal women. Each of these three studies categorizes the patients' risk of fragility fracture by BMD into a low, intermediate or higher risk group and assigns the study bisphosphonate accordingly. The threshold for the intermediate group in the ARIBON trial (T score = -1.0 to -2.5) differs slightly from that of the other two studies (T score = -1.0 to -2.0), and each of the three studies randomized the intermediate group to bisphosphonate or not. The studies each use an oral bisphosphonate, risedronate or ibandronate, in doses and schedules that are US Food and Drug Administration (FDA) approved for the prevention and treatment of postmenopausal osteoporosis. These three studies directly test whether an existing regimen for managing bone health is sufficient to manage BMD in postmenopausal women with breast cancer receiving adjuvant AI therapy. All three studies are of short duration (2 years) and are powered for changes in BMD, a surrogate for fracture risk. These studies were not designed to assess changes in fracture rates or in the risk of breast cancer recurrence. The changes in BMD in these three studies are outlined in Table 1 and are generally positive, demonstrating that the oral bisphosphonates are able to preserve bone mass in the setting of adjuvant anastrozole.

The use of oral bisphosphonate therapy has been well established as an efficacious means of managing BMD in postmenopausal osteoporosis [4]. Both the ARIBON and SABRE trials demonstrated that the patients receiving oral bisphosphonate therapy experienced either stabilization of or an increase in BMD at 2 years. In the ARBI study, however, there was evidence of slight bone

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Table 1. Changes in bone mineral density in the ARBI, ARIBON and SABRE trials

Study (accrual)	Osteoclast inhibitor ^a	Percentage change in BMD at 2 years ^b							
		Lumbar spine				Hip			
		Low risk	Intermediate risk on no bisphosphonate	Intermediate risk on bisphosphonate (P value)	High risk	Low risk	Intermediate risk on no bisphosphonate	Intermediate risk on bisphosphonate (P value)	High risk
ARBI [1] (n = 213)	Risedronate 35 mg weekly	(-) 2.5	(-) 1.5	(+) 5.7 (0.006)	(+) 6.6	(-) 5.7	(-) 3.9	(+) 1.6 (0.037)	(-) 1.9
ARIBON [2] (n = 131)	Ibandronate 150 mg monthly	(-) 4.79	(-) 3.22	(+) 2.98 (<0.01)	(+) 3.52	(-) 3.72	(-) 3.90	(+) 0.60 (<0.01)	(+) 2.49
SABRE [3] (n = 234)	Risedronate 35 mg weekly	(-) 2.1	(-) 1.8	(+) 2.2 (<0.0001)	(+) 3.0	(-) 0.4	(-) 1.1	(+) 1.8 (<0.0001)	(+) 2.0

Percentage change in bone mineral density (BMD) from baseline in postmenopausal women with early-stage breast cancer receiving adjuvant anastrozole with or without oral bisphosphonate therapy. ^aAll patients received calcium + vitamin D. ^bLow risk, study arm that is at low risk of osteoporotic fracture (anastrozole alone); intermediate risk, study arm that is at intermediate risk for osteoporotic fracture (anastrozole with bisphosphonate or not); high risk, study arm that is at higher risk for osteoporotic fracture (anastrozole and bisphosphonate). (+), increase; (-), decrease.

loss in the hip of those in the higher risk category receiving risedronate, and the difference between the two arms in the intermediate group was modest. The difference between hip BMD in the intermediate group therapies may relate to the ARBI sample size, which was based on the expected differences between the randomized groups. Thirty-six patients per arm were planned for the hip BMD analysis; at the 2-year analysis, however, the intermediate risk arm had 26 patients in the anastrozole plus risedronate arm and 21 patients in the anastrozole only arm. Factors that may have also affected the results include poor compliance with bisphosphonate therapy, although the ARBI trial included compliance assessment at each follow-up visit and missed tablets were reported by <10% of the study patients. Compliance is a concern with oral bisphosphonate therapy, as was shown in a cohort study of 8,822 women prescribed risedronate (daily or weekly) in which 31% of the patients were noncompliant after 1 year of treatment [5]. Compliance and persistence rates may vary internationally; the compliance with oral bisphosphonate at 1 year appears to vary between 58 and 74% in the United States, the United Kingdom and France [6].

Zoledronic acid and the intravenously administered form of ibandronate are FDA approved for the management of low bone mass. Intravenous administration within the medical office assures the clinician confirmation of drug delivery. The data supporting the use of intravenous bisphosphonate therapy in the management of AI-induced bone loss in women receiving an AI for early-stage HR-positive breast cancer includes zoledronic acid 4 mg administered every 6 months for 3 to 5 years [7-9]. This bisphosphonate regimen has demonstrated the ability to maintain bone mass in this setting. It is notable that the FDA-approved dosing of zoledronic acid in the management of low bone mass is 5 mg annually when treating osteoporosis and is 5 mg every 2 years

when treating postmenopausal osteopenia, and that Brown and colleagues demonstrated a 4 to 5% increase in BMD at 3 years with a single zoledronic acid dose of 4 mg in patients with osteopenia after cancer therapy given with curative intent [10]. The optimal dose and interval of zoledronic acid to manage BMD in the setting of AI therapy have not been defined.

The clinical trials investigating women at risk for chemotherapy-induced amenorrhea have studied both oral and intravenous bisphosphonates. The results of these studies have for the most part demonstrated that the bisphosphonates preserve BMD [11]. One phase III study of risedronate 35 mg weekly versus placebo in this younger patient population, however, demonstrated that BMD loss in the lumbar spine and hip at 1 year was similar in both arms [12]. Although the ARBI, ARIBON, and SABRE trials have demonstrated that bisphosphonates dosed as the FDA has approved for the treatment or prevention of postmenopausal osteoporosis can control loss of BMD in the setting of adjuvant AI use, the study by Hines and colleagues raises the question of whether the bone loss associated with chemotherapy-induced amenorrhea may respond less well to risedronate 35 mg weekly. Longer follow-up and additional studies will shed light on the management of BMD in this younger patient population.

In conclusion, when managing patients with breast cancer receiving adjuvant AI therapy, the bisphosphonates may be viewed as a supportive therapy to treat or prevent osteoporosis. The data support treating individuals with osteoporosis, but the threshold for initiating pharmacologic interventions for osteopenia is less well defined. The ARBI study presents clinically useful data on the management of bone mass in women with breast cancer receiving adjuvant AI therapy. In addition to managing BMD, adjuvant bisphosphonate therapy may provide antitumor effects. Studies

investigating a range of adjuvant bisphosphonate regimens for their anticancer effects are ongoing, and their results are eagerly awaited.

Abbreviations

AI, aromatase inhibitor; BMD, bone mineral density; FDA, US Food and Drug Administration; HR, hormone receptor.

Competing interests

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References

1. Markopoulos C, Tzoracoleftherakis E, Polychronis A, Venizelos B, Dafni U, Xepapadakis G, Papadiamantis J, Zobolas V, Mitsizis J, Kalogerakos K, Sarantopoulou A, Siasos N, Koukouras D, Antonopoulou Z, Lazarou S, Gogas H: **Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: results from the ARBI prospective clinical trial.** *Breast Cancer Res* 2010, **12**:R24.
2. Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R, Horsman JM, Brown JE, Hannon RA, Coleman RE: **Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer.** *Clin Cancer Res* 2008, **14**:6336-6342.
3. Van Poznak C, Hannon RA, Mackey JR, Campone M, Apffelstaedt JP, Clack G, Barlow D, Makris A, Eastell R: **Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial.** *J Clin Oncol* 2010, **28**:967-975.
4. Chapurlat RD, Delmas PD: **Drug Insight: bisphosphonates for postmenopausal osteoporosis.** *Nat Clin Pract Endocrinol Metab* 2006, **2**:211-219.
5. Penning-van Beest FJA, Erkens JA, Olson M, Herings RM: **Determinants of non-compliance with bisphosphonates in women with postmenopausal osteoporosis.** *Curr Med Res Opin* 2008, **24**:1337-1344.
6. Cramer JA, Lynch NO, Gaudin A-F, Walker M, Cowell W: **The effect of dosing frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women: a comparison of studies in the United States, the United Kingdom, and France.** *Clin Ther* 2006, **28**:1686-1694.
7. Brufsky AM, Bosserman LD, Caradonna RR, Haley BB, Jones CM, Moore HC, Jin L, Warsi GM, Ericson SG, Perez EA: **Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results.** *Clin Breast Cancer* 2009, **9**:77-85.
8. Gnant M, Mlineritsch B, Lushin-Ebengreuth G, Kainberger F, Kässmann H, Piswanger-Sölkner JC, Seifert M, Ploner F, Menzel C, Dubsy P, Fitzal F, Bjelic-Radicic V, Steger G, Greil R, Marth C, Kubista E, Samonigg H, Wohlmuth P, Mittlböck M, Jakesz R. Austrian Breast and Colorectal Cancer Study Group (ABCSCG): **Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSCG-12 bone-mineral density substudy.** *Lancet Oncol* 2008, **9**:840-849.
9. Hines SL, Sloan JA, Atherton PJ, Perez EA, Dakhil SR, Johnson DB, Reddy PS, Dalton RJ, Mattar BJ, Loprinzi CL: **Zoledronic acid for treatment of osteopenia and osteoporosis in women with primary breast cancer (BC) undergoing adjuvant aromatase inhibitor (AI) therapy [abstract 2103].** *Cancer Res* 2009, **69**:626s.
10. Brown JE, Ellis SP, Lester JE, Gutcher S, Khanna T, Purohit OP, McCloskey E, Coleman RE: **Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid.** *Clin Cancer Res* 2007, **13**:5406-5410.
11. Saad F, Adachi JD, Brown JP, Canning LA, Gelmon KA, Josse RG, Pritchard KI: **Cancer treatment-induced bone loss in breast and prostate cancer.** *J Clin Oncol* 2008, **26**:5465-5476.
12. Hines SL, Mincey BA, Sloan JA, Thomas SP, Chottiner E, Loprinzi CL, Carlson MD, Atherton PJ, Salim M, Perez EA: **Phase III randomized, placebo-controlled, double-blind trial of risedronate for the prevention of bone loss in premenopausal women undergoing chemotherapy for primary breast cancer, 2009.** *J Clin Oncol* 2009, **27**:1047-1053.

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