

## LETTER to the EDITOR

# Does Zoledronic Acid Have Additive Effect on Suppression of Plasma Estrogen Levels ?

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### Dear Editor

Obesity has been associated with abnormally high expression of the enzyme aromatase in the breast, increased local estrogen production and predisposition to the cancer and recurrence. In postmenopausal women, fat tissue is the major source of estrogens, thus higher aromatase enzyme levels in obese patients can increase the estrogen levels. On these grounds, expression of aromatase enzyme increased with high body mass index (BMI), may influence the effects of aromatase inhibitors. Folkerd et al. (2012) recently published an article about the effect of aromatase inhibitors on suppression of plasma estrogen levels according to the BMI in patients with breast cancer. The authors suggest that the plasma estrogen levels were associated with BMI and letrozole compared to anastrozole reduced estrogen levels by an additional 43%. We have some comments about the additive effect of zoledronic acid on aromatase activity.

Intravenous bisphosphonate zoledronic acid has been evaluated in adjuvant breast cancer clinical trials. In the Zometa-Femara Ajuvant Synergy Trial (ZFAST) and ZOFAS (Zoledronic acid in the prevention of cancer treatment-induced bone loss in postmenopausal women receiving letrozole as adjuvant therapy for early breast cancer), there were 35% fewer breast cancer recurrences (Brufsky et al., 2007; Eidtmann et al., 2010). In another study, patients with early-stage breast cancer in the Austrian Breast Cancer Study Group trial 12 (ABCSG-12), the addition of zoledronic acid to adjuvant endocrine therapy significantly improves disease-free survival and fewer locoregional recurrences and contralateral breast cancers in premenopausal patients (Gnant et al., 2009). Zoledronic acid therapy prevents bone loss associated with aromatase inhibitors in premenopausal and postmenopausal breast cancer patients (Brufsky et al., 2007; Gnant et al., 2007; 2008). Thus, zoledronic acid have been widely used in osteoporotic patients, for the protective effect of bone loss of aromatase inhibitors and in the adjuvant treatment of early breast cancer patients in recent years.

The significant benefit of zoledronic acid is by inhibition of tumor-cell adhesion, invasion, proliferation and inducing apoptosis in cell lines (Gnant et al., 2009). Also zoledronic acid can stimulate antitumor immune reactions and exert antiangiogenic effects (Kunzmann et al., 2000; Santini et al., 2007). In a recent trial, Schech et al. (2012) found that the combination of zoledronic

acid and letrozole lead to increased inhibition of aromatase enzyme compared to letrozole alone. Zoledronic acid can inhibit aromatase activity by inhibition of serine phosphorylation. This study showed that zoledronic acid potentiates the aromatase inhibition of letrozole. In ABCSG-12 trial, zoledronic acid compared to placebo improved disease-free survival in normal weight and overweight patients (Pfeiler et al., 2011).

In the light of the recent publications, zoledronic acid may have additive effect on the inhibition of aromatase enzyme. On these grounds, it is intriguing to wonder about the distribution of zoledronic acid usage in the study of Folkerd et al. (2012).

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