

apy: there are benefits to stopping and risks to continuing with respect to breast cancer.

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## Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

**TO THE EDITOR:** Gnant et al. (Feb. 12 issue)<sup>1</sup> report on the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) (ClinicalTrials.gov number, NCT00295646), which looked at the use of goserelin plus either tamoxifen or anastrozole with or without zoledronic acid in premenopausal women with breast cancer. The authors conclude that the addition of zoledronic acid improved disease-free survival and that treatment with tamoxifen and treatment with anastrozole were associated with similar rates of disease-free survival. However, a separate analysis of the group of patients who received anastrozole without zoledronic acid would be of interest.

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1. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;360:679-91.

**TO THE EDITOR:** Gnant et al. report a 4-year rate of 90.8% for disease-free survival in the group of premenopausal women with breast cancer who received endocrine therapy alone and a rate of 94.0% in the group that received endocrine therapy plus zoledronic acid. Data from this trial that were presented at the American Society of Clinical Oncology meeting in 2008 showed that the effect of zoledronic acid was driven almost exclusively by the findings in the cohort of patients who received anastrozole, whereas little effect was discernible for the patients who received tamoxifen. With only 137 events contributing to these analyses, the test for interaction comparing the effectiveness of zoledronic acid between the anastrozole group and the tamoxifen group is expected

to be nonsignificant. What was the effect of zoledronic acid on the anastrozole and tamoxifen groups?

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**TO THE EDITOR:** Gnant et al. describe the results of the combination of tamoxifen plus goserelin; however, this combined therapy is not a standard option for the typical premenopausal patient with breast cancer enrolled in this study. In most centers, outside the context of a clinical trial, such patients would be offered 5 years of tamoxifen plus or minus chemotherapy,<sup>1</sup> with the possible addition of ovarian ablation for women under the age of 35 years who did not have chemotherapy-induced amenorrhea.<sup>2,3</sup> The combination of ovarian suppression and tamoxifen is being prospectively addressed in the Suppression of Ovarian Function Trial (SOFT) (ClinicalTrials.gov number, NCT00066690). In addition, the duration of the tamoxifen exposure (3 years) cannot be considered a standard, level I, evidence-based form of adjuvant hormonal therapy.

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**TO THE EDITOR:** Gnant et al. did not compare disease-free survival between the group of patients who received goserelin plus tamoxifen plus zoledronic acid and the group that received goserelin plus anastrozole plus zoledronic acid. An uneven distribution of HER-2/neu overexpression among the groups might have influenced the outcomes of this study. Predictive markers such as HER-2/neu overexpression should be included in the analysis.

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**TO THE EDITOR:** In Table 2 of the article by Gnant et al., there is a trend favoring tamoxifen with respect to distant recurrence and death. In the two groups of patients who received endocrine therapy, there were 15 deaths in the tamoxifen group, as compared with 27 in the anastrozole group (hazard ratio, 1.80; 95% confidence interval, 0.95 to 3.38). The P value of 0.70 for overall survival (as presented in Fig. 2E of the article) is not understandable; we would expect a P value of 0.07 on the basis of the 95% confidence interval and event numbers.

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**TO THE EDITOR:** Gnant et al. report that six doses of zoledronic acid prolonged disease-free survival in premenopausal patients with breast cancer who were undergoing adjuvant endocrine therapy. Bisphosphonates are commonly prescribed in association with vitamin D supplementation. However, there is no mention as to whether vitamin D was prescribed to patients in this trial.

Vitamin D decreases the cellular proliferation of cancer cells,<sup>1</sup> so that vitamin D supplementation represents a potential confounder in the interpretation of the study results. In addition, hypovitaminosis D is relatively common in premenopausal women,<sup>2</sup> and this condition may be worsened by estrogen deprivation.<sup>3</sup> Vitamin D deficiency in early breast cancer has been found to be associated with an increased risk of distant recurrence and death.<sup>4</sup>

On these grounds, it would be interesting to know whether any of the patients who were treated with zoledronic acid received vitamin D supplementation, whether these patients had a different outcome, and whether there was an interaction in terms of outcome between zoledronic acid and anastrozole.

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**TO THE EDITOR:** The pharmacokinetic properties of zoledronic acid do not support the hypothesis of Gnant et al. that this drug has antitumor effects in tissue other than bone. After intravenous administration, bisphosphonates spread in calcified and noncalcified tissues, but their levels decline quickly in noncalcified tissues, and the decline is proportionate to the decrease in the plasma concentration.<sup>1,2</sup> In animal models, repeated injections of zoledronic acid (every 4 days) were required to reduce the number of metastatic foci outside bone, in which zoledronic acid did not induce apoptosis.<sup>3</sup>

Bone marrow-derived mesenchymal stem cells are recruited to the stroma of developing tumors.

Karnoub et al.<sup>4</sup> demonstrated that mesenchymal stem cells greatly increase the metastatic potential of breast-cancer cells by secreting chemokines and growth factors that sustain breast-cancer migration, invasion, and metastases. In this regard, we have recently shown that zoledronic acid affects the ability of mesenchymal stem cells to secrete angiogenic factors that promote breast-cancer metastasis.<sup>5</sup> We propose that the antitumor activity of zoledronic acid in patients with breast cancer is related to its action on mesenchymal stem cells within the bone marrow microenvironment.

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**THE AUTHOR REPLIES:** In response to Wenz, Gelber and Aebi, Katz et al., Li and Dong, and Reimer and Gerber: according to St. Gallen and National Comprehensive Cancer Network guidelines, goserelin plus tamoxifen is an accepted treatment for premenopausal patients with endocrine-responsive breast cancer, and luteinizing hormone-releasing hormone agonists alone are associated with a strong trend toward reduced rates of recurrence and death.<sup>1</sup> In the ABCSG-12 study, the selection of 3 years of endocrine therapy was based on the findings of the ABCSG-5 trial (ClinicalTrials.gov number, NCT00309478) (which examined 3 years of goserelin, then 5 years of tamoxifen).<sup>2</sup> However, 5 years of continuous endocrine therapy may not be necessary in this low-risk population, since it would be difficult to improve the 98.2% 4-year overall survival achieved in the group receiving zoledronic acid in the ABCSG-12 trial. We agree that long-term follow-up of SOFT and Triptorelin with Exemestane on Tamoxifen

(TEXT) (NCT00066703) may provide more definitive guidance on the use of aromatase inhibitors in premenopausal patients with breast cancer.

The ABCSG-12 study was designed and powered to show whether the addition of zoledronic acid to endocrine therapy improved outcomes, as compared with endocrine therapy alone. A specific interaction test did not reveal any difference in the treatment effect between the group receiving anastrozole plus zoledronic acid and the group receiving tamoxifen plus zoledronic acid. Therefore, at this time, it is not possible to conclude that the effect of zoledronic acid was driven primarily by the findings in one cohort. Longer follow-up of the zoledronic acid effect may help to determine whether meaningful differences exist.

Reimer and Gerber are correct in pointing out that there was a nonsignificant trend favoring tamoxifen over anastrozole for survival, and both P values in Figure 2E should be 0.07 rather than 0.70. (The article has been corrected at NEJM.org.)

In response to Li and Dong: we did not prospectively determine the HER-2/neu status of patients in our study. However, since patients underwent randomization, the proportion of HER-2/neu-positive patients is likely to have been balanced among the study groups and is unlikely to have confounded the trial outcomes.

In response to Berruti et al.: vitamin D levels and vitamin D supplementation were not part of our protocol and therefore were not prospectively recorded. However, we agree that this could be an important factor and should be elucidated in future trials of adjuvant bisphosphonates.

We agree with De Luca and Normanno that the antitumor effects of zoledronic acid may be mediated by preventing the secretion of angiogenic factors by mesenchymal stem cells in bone marrow. This is entirely consistent with the idea that zoledronic acid makes the bone-and-marrow microenvironment less favorable "soil" for tumor-cell growth. One hypothesis is that bone may provide a sanctuary for dormant micrometastases that may later seed distant metastases. Preliminary clinical data suggest that the antitumor activity of zoledronic acid may include the inhibition of angiogenesis, immunostimulatory effects through the activation of gamma delta T cells,<sup>3</sup> and a reduction in the number of disseminated tumor cells in bone marrow.<sup>4</sup> In addition, recent results from the neoadjuvant subgroup analysis of the Adjuvant

Zoledronic Acid to Reduce Recurrence (AZURE) (NCT00072020) trial indicate that zoledronic acid has direct antitumor activity.<sup>5</sup> Therefore, stimulation of a wide array of antitumor effects by zoledronic acid may inhibit disease progression in areas other than bone in patients with breast cancer.

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## Long-Term Consequences of Kidney Donation

**TO THE EDITOR:** The outcomes for living kidney donors, shown in the study by Ibrahim et al. (Jan. 29 issue),<sup>1</sup> are reassuring. Key strengths of the study are the large sample and the long follow-up. However, limitations include a highly selected and ethnically homogeneous population and the lack of acknowledgment that living donors today have an increasing number of health risk factors such as obesity. Also missing are considerations of the effect of unique regional practices and rates of end-stage renal disease (ESRD), socioeconomic influences, access to health care, educational level, and lifestyle choices. We would argue that the good survival and lower overall rate of ESRD as compared with the rates in the general population may have been due to the optimal condition of the donors at the time of their donation. The rate of ESRD should have been reported according to geographic area, since the rate varies substantially across the country. Furthermore, the ideal control group is not the general population but a group of people living in the same area who have been evaluated as candidates for donation but who did not donate. Even with the excellent research design, this study cannot be taken as the final word. Potential donors of nonwhite background need to be very carefully screened and counseled.<sup>2,3</sup>

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**TO THE EDITOR:** As a primary care physician and recent nondirected kidney donor, I found the article by Ibrahim et al. to be generally reassuring, yet also disconcerting, about health care after donation. Of the 255 donors who voluntarily underwent examinations, 82 (32%) had blood pressures higher than 140/90 mm Hg. Of these, 19 (23%) had undiagnosed hypertension or were not taking antihypertensive medicine, and another 12 (15%) had poorly controlled hypertension despite taking antihypertensive medicine. Thus, 38% of examined donors with hypertension had poorly controlled blood pressure. Of the 11 donors known to have ESRD, 3 of the 7 with a known cause (43%) had hypertensive nephropathy. On average, systolic blood pressure increases by 5 mm Hg after donation.<sup>1</sup> Thus, it can be anticipated that a few donors may have a much higher increase and that hypertensive nephropathy will develop in some of them. Health care for donors is provided primarily by providers other than those in transplantation centers; these clinicians must do better to prevent and manage hypertension and to prevent hypertensive nephropathy. I am aware of only one guideline for people with solitary kid-