

## Chemotherapy in Older Women with Breast Cancer

**TO THE EDITOR:** Muss et al. (May 14 issue)<sup>1</sup> report that standard adjuvant chemotherapy is superior to capecitabine in older women with early-stage breast cancer. However, the authors neglect to mention that adjuvant radiotherapy in patients with positive axillary nodes affects relapse-free survival.<sup>2,3</sup>

The use of chest-wall and regional lymph-node irradiation after mastectomy and chemotherapy is recommended in women with four or more positive axillary lymph nodes, and it is recommended for strong consideration in women with one to three positive axillary lymph nodes.<sup>3,4</sup> Prophylactic chest-wall irradiation in these patients substantially reduces the risk of local recurrence.<sup>5</sup>

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**TO THE EDITOR:** Muss et al. found standard adjuvant chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide plus doxorubicin) to be superior to capecitabine in terms of relapse-free survival and overall survival. An unplanned subgroup analysis revealed that the difference between treatment groups was significant in patients with hormone-receptor-negative tumors but not in patients with hormone-receptor-positive tumors. However, there is a smaller benefit from standard adjuvant chemo-

therapy in patients with hormone-receptor-positive tumors than in patients with hormone-receptor-negative tumors.<sup>1</sup> Thus, to gain significance in this subgroup with a low-risk profile (mostly T1 or T2 tumors with zero to three positive lymph nodes), more patients are needed to observe the difference between treatment groups in a short follow-up time (2.4 years). Outcomes in patients with hormone-receptor-positive tumors require separate analyses.

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1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-717.

**THE AUTHORS REPLY:** Zeng notes that radiation therapy after mastectomy in patients with positive lymph nodes improves survival. Indeed, we did "neglect" irradiation after mastectomy in our analysis. Such neglect is conventional in analyzing breast-cancer trials, and for good reason. Patients were not randomly assigned to irradiation or primary surgery. These doctor-patient choices are based at least in part on clinical characteristics. They might be considered as covariates in a multivariate analysis of treatment effect, but even this would be questionable because they are highly correlated with clinical characteristics that are already included in the analysis. Although it is true that some management issues may affect outcome, they are usually balanced across treatment groups — as is the case in our study. When they are not balanced, they are subsumed in the group's therapeutic strategy as part of an intention-to-treat analysis. Therefore, the conventional approach in medical research is to not consider patient treatment issues in comparisons of treatment groups.

We agree with Dizdar and colleagues that chemotherapy is associated with less benefit in hormone-receptor-positive breast cancer than in hormone-receptor-negative breast cancer. Indeed, an earlier analysis of our Cancer and Leukemia

Group B (CALGB) data<sup>1</sup> shows exactly this finding, and it led to our subgroup analysis in the present study. Moreover, these CALGB data show that chemotherapy's benefit occurs in the first few years after treatment. Regarding the "relatively short follow-up time" in our study, it is most unlikely that any difference will emerge in the hormone-receptor-positive subgroup with longer follow-up. Regarding the need for more patients, in view of the low relapse rate among patients with hormone-receptor-positive primary tumors, it would take thousands of patients to try to show a benefit, and any benefit would probably be very small. Such a large trial in this population would be almost impossible to complete. An adjuvant trial involving women 65 years of age or older that has just completed accrual of 1400 patients

compares ibandronate with ibandronate and capcitabine.<sup>2</sup>

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2. ClinicalTrials.gov. Study in elderly patients with early breast cancer (ICE). (Accessed August 13, 2009, at <http://clinicaltrials.gov/ct2/show/NCT00196859>.)

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## Immunologic Aspects of Chronic Obstructive Pulmonary Disease

**TO THE EDITOR:** Cosio et al. (June 4 issue)<sup>1</sup> present data that will stimulate the study of the role of autoimmunity in the pathogenesis of chronic obstructive pulmonary disease (COPD). However, we think that research efforts focusing on the mechanisms of autoimmunity in COPD are not of paramount importance in smokers and patients with COPD, at least from a practical point of view. First, we believe that tobacco smoke can affect individual persons differently, just as alcohol can affect persons who abuse alcohol differently and silica dust can affect quarry workers differently. Second, it is also clear that genetic factors as well as the quantity of inhaled smoke can have a fundamental influence on the devel-

opment of COPD. Third, and most important, even if it were possible to identify smokers with the highest risk of COPD, other serious consequences of smoking such as cardiovascular or neoplastic diseases need to be taken in consideration.

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## Veterans Affairs Diabetes Trial — Corrections

**TO THE EDITOR:** The Supplementary Appendix in which we provided additional information related to our article (Jan. 8 issue)<sup>1</sup> contains some errors. In both Appendix 1 and Appendix 2, the heading "6 Year Event Rate" should have read "6-Year Event-free Rate." We thank the reader who detected this error.

In addition, on further examination of the data on albuminuria from the Veterans Affairs Diabe-

tes Trial, we found that the data set that we used to evaluate the progression of disease was constructed improperly. As a result, the rates of progression to microalbuminuria and macroalbuminuria were reported in Table 3 of our article as being lower than they actually were. An error in the computer code resulted in the replacement of post-randomization albumin-to-creatinine ratios with the baseline albumin-to-creatinine ratio