

Paclitaxel plus Bevacizumab for Metastatic Breast Cancer

TO THE EDITOR: On the basis of an increase in progression-free survival of 5.9 months, Miller et al. (Dec. 27, 2007, issue)¹ imply that the addition of bevacizumab to paclitaxel is a significant advance in the treatment of metastatic breast cancer. However, progression-free survival is an unreliable measure of benefit in metastatic cancer, and patients given bevacizumab do not live longer than patients given paclitaxel alone. Furthermore, it is questionable to cite response rates in phase 3 studies, since response rates are a means of looking for active new agents in phase 2 studies. Finally, there are no data that justify a dose of bevacizumab greater than 3 mg per kilogram of body weight in phase 3 studies²; a dose that adds to cost and potential toxicity. Crucially, the data reported by Miller et al. reveal no correlation between progression-free survival or response rates and overall survival or quality of life. What, then, are the benefits of this treatment?

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TO THE EDITOR: The advantage in progression-free survival for bevacizumab plus paclitaxel, reported by Miller et al., might be overestimated because of attrition bias¹: since data on progression-free survival were censored for patients in whom nonprotocol therapy was initiated, systematic differences between the comparison groups in the loss of participants from the study may have set in. Information on how many patients started nonprotocol therapy, whether the distribution of this type of censoring was similar in the two groups, and whether the nonprotocol therapies were similar should therefore be reported.

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Dr. Gridelli reports receiving consulting and lecture fees from Roche. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Haines and Miklos raise questions about the goals of therapy for metastatic breast cancer. Our goal was to maximize disease control and quality of life, thereby sparing patients for as long as possible from symptoms of progressive breast cancer, toxic effects of subsequent therapies, and the psychological burden and uncertainty that come with progression. Since patients enrolled in the E2100 trial had few symptoms, an improvement in quality of life could not be expected. In addition, patients frequently receive multiple effective chemotherapy regimens for metastatic breast cancer, potentially obscuring any survival benefit from that associated with therapy administered in the first-line setting. For these reasons, we selected progression-free survival as the end point that would most reflect any benefits of first-line therapy. Since E2100 had only an 80% power to detect a 7-month improvement in overall survival, it is unlikely that more modest improvements would reach statistical significance. In our view, the improvement in 1-year survival with the addition of bevacizumab (81.2% vs. 73.4%, $P=0.01$) confirms our original conclusion.¹

The dose of bevacizumab used in E2100 was based on a preliminary dose-finding trial involving patients with refractory breast cancer.² We agree that the optimal dose of bevacizumab has not been well defined. The bevacizumab (Avastin) and docetaxel (AVADO) trial, which randomly assigns women to receive one of two doses of bevacizumab (15 mg per kilogram or 7.5 mg per kilogram) every 3 weeks or placebo in combination with docetaxel as initial chemotherapy for metastatic breast cancer, will shed light on this critical issue.

Rossi et al. ask about the effects of attrition bias, censoring, and nonprotocol therapy. We

found no significant differences between the study groups in compliance with protocol assessment or nonprotocol therapy administered before progression. Since censoring is affected by differences in progression-free survival, comparisons are not very meaningful. Nonetheless, we found no major differences in the number of patients for whom data were censored (31 vs. 10) or the median time from registration to censoring (29.4 months vs. 16.8 months). Finally, we found no differences in the reasons for treatment discontinuation.

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Platelet Activation and Atherothrombosis

TO THE EDITOR: In their review of platelet activation and atherothrombosis, Davì and Patrono (Dec. 13, 2007, issue)¹ state that “the clinical benefit associated with P2Y₁₂ blockade by clopidogrel in patients receiving aspirin is relatively modest and inconsistent.” However, combining aspirin and clopidogrel is beneficial in certain subgroups. In one study, after percutaneous coronary intervention, combination therapy for 1 year was associated with a 26.9% relative reduction in the combined risk of death, myocardial infarction, or stroke.² The addition of clopidogrel (300 mg in a loading dose, then 75 mg daily) to aspirin also improved patency rates for the infarct-related artery and reduced ischemic complications in patients with ST-segment elevation.³ The composite end point of arterial occlusion, death, or recurrent myocardial infarction in the study by Sabatine et al.³ was reduced by 36% with clopidogrel. Combination therapy also reduced the composite end point of death, reinfarction, or stroke as well as all-cause mortality and reinfarction among 45,852 patients presenting with an acute myocardial infarction.⁴ The clinical benefits of the combination therapy were not associated with an increased risk of bleeding. Thus, the beneficial role of dual antiplatelet therapy should not be underestimated.

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THE AUTHORS REPLY: In response to Kapoor’s comments, the relative risk reduction of major vascular events associated with the combination of clopidogrel and aspirin, as compared with single antiplatelet therapy, is relatively modest and inconsistent in the major areas of high cardiovascular risk (Fig. 1).²⁻⁴ The additional benefit of dual antiplatelet therapy versus aspirin alone is only a fraction of the benefit associated with aspirin versus placebo in the same clinical setting.^{1,5} In our article, we also suggest that the role of adenosine diphosphate (ADP) in atherothrombosis may have been underestimated on the basis of trials of ticlopidine and clopidogrel because of incomplete and variable blockade of ADP-induced platelet aggregation by these drugs. The results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON—TIMI) 386 are consistent with this hypothesis.