CORRESPONDENCE

Bevacizumab in Neoadjuvant Treatment for Breast Cancer

TO THE EDITOR: The results of two studies, by von Minckwitz et al. (GeparQuinto [GBG44] trial; ClinicalTrials.gov number, NCT00567554)[1] and Bear et al. (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-40 trial, NCT00408408)[2] (Jan. 26 issue), indicate an additional value of bevacizumab in neoadjuvant chemotherapy in patients with breast cancer. However, previous clinical studies have shown discrepant results for bevacizumab in the treatment of metastatic breast cancer. As suggested in the editorial in the same issue,[3] the additional value of bevacizumab may be chemotherapy-specific. More important, we believe that the timing of bevacizumab administration (before or after chemotherapy) may have a considerable effect on the delivery of chemotherapy to tumors,[4] leading to differences in the efficacy of combination therapy. Data are lacking from clinical trials in which patients with cancer are randomly assigned to different administration schedules. Until these data are available, observational data may be valuable to elucidate whether drug scheduling affects the efficacy of combination therapy. We wonder in which sequence bevacizumab and chemotherapy were administered in the study by Bear et al.[2] To gain more insight into scheduling as a potential contributing factor in efficacy, we think that the sequence of as well as the interval between bevacizumab and chemotherapy administration should be clearly defined for each clinical trial.

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No potential conflict of interest relevant to this letter was reported.

1. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366:299-309.
2. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012;366:310-20.
3. Montero AJ, Vogel C. Fighting fire with fire: rekindling the bevacizumab debate. N Engl J Med 2012;366:374-5.
4. Van der Veldt AA, Lubberink M, Bahce I, et al. Rapid decrease in delivery of chemotherapy to tumors after anti-VEGF therapy: implications for scheduling of anti-angiogenic drugs. Cancer Cell 2012;21:82-91.

TO THE EDITOR: In the article on the NSABP B-40 trial of neoadjuvant chemotherapy with or without bevacizumab, a clear definition of hormone-receptor–positive disease was not provided, whereas in the accompanying article on the GBG44 trial, hormone-receptor–positive disease was defined with the use of a 10% cutoff on immunohistochemical staining. Hence, one cannot rule out the possibility that a significant number of

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cases of hormone-receptor–positive disease in the NSABP B-40 trial, which were defined by individual investigators, could have been classified as triple-negative with the use of the criterion of the GBG44 trial (<10% of cells positive for either estrogen-receptor protein or progesterone-receptor protein), leading to a change in the assessment of the effect of bevacizumab in patients with hormone-receptor–positive disease versus patients with triple-negative disease. The differences between the two trials with respect to rates of pathological complete response, defined as the absence of invasive disease in the breast, irrespective of nodes, were in favor of bevacizumab (16.5% without bevacizumab vs. 20.5% with bevacizumab in the GBG44 trial, and 28.2% vs. 34.5% in the NSABP B-40 trial), but neither trial revealed a significant difference when complete response inclusive of both breast and lymph nodes was assessed.[1] Future trial designs should include a more precise definition and quantitative assessment of hormone-receptor–positive disease,[2] in addition to agreement on a standardized definition of pathological complete response.

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Dr. Somlo reports being a member of the National Comprehensive Cancer Network breast-cancer panel and receiving research support and speaking fees from Genentech. No other potential conflict of interest relevant to this letter was reported.

1. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010;28:3784-96.
2. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007;25:4414-22.

TO THE EDITOR: The editorial on the NSABP B-40 and the GBG44 trials correctly contends that the bevacizumab controversy hinges on whether certain surrogate end points are useful for predicting overall survival and drug efficacy. The authors of the editorial raise two key questions: is progression-free survival a surrogate end point for metastatic breast cancer, and is pathological complete response in the neoadjuvant setting a surrogate for overall survival? Data from 17 clinical trials of bevacizumab show that the answer to the first question is no.[1] In the neoadjuvant setting, the data from the NSABP B-40 and GBG44 trials are so distant from overall survival as to be clinically unconvincing. Rates of pathological complete response in the breast alone are hardly appropriate as compared with the more clinically meaningful rate of pathological complete response in breast and axillary nodes. Extensive data[1] and recent articles in the *Journal*[2,3] all indicate that bevacizumab has marginal clinical efficacy. The statement that the decision by the Food and Drug Administration (FDA) "to withdraw the indication of bevacizumab for metastatic breast cancer will be further called into question" is a distraction. Patient well-being requires better clinical data, not more debate.

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No potential conflict of interest relevant to this letter was reported.

1. Haines IE, Gabor Miklos GLG. Time to mandate data release and independent audits for all clinical trials. Med J Aust 2011; 195:575-7.
2. Sekeres MA. The Avastin story. N Engl J Med 2011;365:1454-5.
3. Carpenter D, Kesselheim AS, Joffe S. Reputation and precedent in the bevacizumab decision. N Engl J Med 2011;365(2):e3.

DR. VON MINCKWITZ AND COLLEAGUES REPLY: We cannot prove van der Veldt and Smit's hypothesis, since we did not capture information on when the patients received bevacizumab in relation to chemotherapy in the GBG44 trial. According to the protocol, the first infusion had to be administered before chemotherapy; thereafter, the sequence was up to the investigator. However, because of the long half-life of bevacizumab, we would not expect that sequence would make a major difference.

A total of 65 of 1948 participants in our study (3.3%) had hormone-receptor levels between 1% and 9%. The rate of pathological complete response in this small cohort was 20.0% without bevacizumab and 33.3% with bevacizumab, which is somewhat lower than that among patients with hormone-receptor levels below 1%, but the absolute difference in pathological complete response was similar to that in the overall cohort of patients with hormone-receptor–negative disease. A significant positive effect of bevacizumab was seen in triple-negative tumors with the use of either definition of hormone-receptor negativity (<10% or <1% of cells positive for either estrogen-receptor protein or progesterone-receptor protein).

Our group just analyzed data from 6377 patients treated in neoadjuvant trials in Germany and recommended the most conservative definition of a pathological complete response (ypT0, ypN0) (i.e., no invasive and no noninvasive residual disease in breast and nodes) to provide the best discrimination between a favorable and an unfavorable long-term outcome. Of note, this conservative definition was used as a primary end point in our study (as requested by Gabor Miklos) and showed a significant difference in pathological complete response.

Studies have repeatedly shown that the pathological complete response correlates best with survival among patients with triple-negative disease.[1,2] This is the subgroup in which we saw the largest effect of bevacizumab. However, we do not recommend extrapolation of data on early neoadjuvant treatment or from treatment of patients with metastatic cancer to the long-term effect of bevacizumab in early breast cancer. We have to await data on overall survival from our study and the NSABP B-40 study, as well as from adjuvant trials (especially those focused on triple-negative breast cancer) to make a final assessment.

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Since publication of their article, the authors report no further potential conflict of interest.

1. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathological complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2011;38:8595.
2. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26:1275-81.

DR. BEAR AND COLLEAGUES REPLY: In response to van der Veldt and Smit's provocative question: we regret that space did not allow us to provide full details about treatment. However, a link to the complete protocol was included and is also available at www.cancer.gov/clinicaltrials/search/view?cdrid=515432&version=healthprofessional. Bevacizumab was administered on day 1 of each of the first six cycles of chemotherapy and, according to the protocol, was initially administered before the chemotherapy drugs (in approximately 250 patients who were randomly assigned to treatment); however, after the second protocol amendment in March 2008, each institution was allowed to follow its own policies regarding the sequence of administration. Whether the timing between the administration of bevacizumab and the infusion of chemotherapy on the same day would affect the delivery of chemotherapy drugs to the tumor, as suggested by van der Veldt and Smit, is uncertain.

Somlo raises an important caveat regarding definitions of hormone-receptor–positive breast cancer. Current pathological guidelines now define the presence of more than 1% of cells that are positive for either estrogen-receptor protein or progesterone-receptor protein on immunohistochemical staining as "positive,"[1] but it could be argued that "weakly positive" tumors with less than 10% of cells that are positive may not be truly hormone-sensitive. As stated, if a significant proportion of the tumors classified as hormone-receptor–positive were in the 1 to 10% range, our results may have been more similar to those in the GBG44 trial. However, assays from cores may not be accurate; in a study by Tamaki et al., concordance rates between cores and surgical specimens were 92.9% for estrogen-receptor positivity and 77.9% for progesterone-receptor positivity.[2] Eventually, molecular analysis of the tissues we obtained before treatment may clarify this issue.

We agree with Gabor Miklos that overall survival is the key end point for including new agents in the treatment of early-stage breast cancer, and we await sufficient events to report on this end point. Pathological complete response in the breast was by design the primary end point for the NSABP B-40 trial. Although it is true that the pathologic status of breast plus nodes is a "stronger" predictor of patient outcomes after neoadjuvant therapy, it is questionable whether nodal status really should be considered a "response" unless the presence of cancer in the nodes has been proved before therapy.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010; 28:2784-95. [Erratum, J Clin Oncol 2010;28:3543.]
2. Tamaki K, Sasano H, Ishida T, et al. Comparison of core needle biopsy (CNB) and surgical specimens for accurate preoperative evaluation of ER, PgR and HER2 status of breast cancer patients. Cancer Sci 2010;101:2074-9.

THE EDITORIALISTS REPLY: In response to Gabor Miklos: we agree that "better clinical data" are needed. Looking at the phase 3 data, we can conclude that there is a variable prolongation of progression-free survival, which has not translated into a significant improvement in overall survival.[1] However, from these data one cannot conclude that progression-free survival is an invalid clinical end point. We do not think that the decision by the FDA to withdraw the indication for bevacizumab in women with breast cancer is a "distraction," but goes to the heart of the matter of surrogate end points.[1] The overall benefit of bevacizumab in metastatic breast cancer appears to be modest. On the basis of data from E2100 (NCT00028990), we have recently found that the use of bevacizumab in metastatic breast cancer is not cost-effective and does not represent a good value for health care dollars.[2] We are hopeful that these controversies will indeed kindle a fire in the research community so that clinical trials are conducted in a smarter and more efficient manner. We also sincerely hope that effective predictive markers, perhaps as suggested by data from A Randomized Phase III Trial to Evaluate Bevacizumab in Combination with Trastuzumab Plus Docetaxel as First-Line Therapy for HER2-Positive Locally Recurrent/Metastatic Breast Cancer (AVEREL, NCT00391092),[3] will advance the use of antiangiogenic agents.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Montero AJ, Escobar M, Lopes G, Gluck S, Vogel C. Bevacizumab in the treatment of metastatic breast cancer: friend or foe? Curr Oncol Rep 2012;14:1-11.
2. Montero AJ, Avancha K, Glück S, Lopes G. A cost-benefit analysis of bevacizumab in combination with paclitaxel in the first-line treatment of patients with metastatic breast cancer. Breast Cancer Res Treat 2012;132:747-51.
3. Gianni L, Romieu G, Lichinitser M, et al. First results of AVEREL, a randomized phase III trial to evaluate bevacizumab (BEV) in combination with trastuzumab (H) + docetaxel (DOC) as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC). In: Program and abstracts of the San Antonio Breast Cancer Symposium, San Antonio, TX, December 6–10, 2011. abstract.

Antenatal Thyroid Screening and Childhood Cognitive Function

TO THE EDITOR: Lazarus and colleagues (Feb. 9 issue)[1] administered levothyroxine to pregnant women who had a serum thyrotropin level above the 97.5th percentile, a serum free thyroxine level below the 2.5th percentile, or both to investigate the potential benefit on later cognitive function in their children. However, it is questionable whether these cutoff values were appropriate, given the known iodine deficiency among young women in the United Kingdom[2] and indeed in a subgroup of women in the trial.[3] If reference ranges derived from iodine-sufficient populations[4,5] had been used, the cutoffs would have been lower for thyrotropin and higher for free thyroxine, thereby increasing the number of women who would have been treated (along with their respective controls). (Incidentally, the units of free thyroxine have been inaccurately converted on page 494 of the article.) Since thyroid dysfunction may have been underdiagnosed, the statistical power to detect a significant difference may have been reduced. Although the authors claim that the study was adequately powered, the calculation may have been invalid, since it was based on a study that was conducted in an iodine-sufficient country (the United States), and the women in that study had more severe thyroid dysfunction (a higher serum thyrotropin level).[6] We consider that these points are pertinent to the interpretation of the results of this trial.