Title
Continued Exploration of Bevacizumab in Breast Cancer

Journal
Annals of Surgical Oncology, 17(2)

ISSN
1534-4681

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Publication Date
2010-02-01

DOI
10.1245/s10434-009-0835-4

Peer reviewed

Ann Surg Oncol (2010) 17:655–656
DOI 10.1245/s10434-009-0835-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

LETTER TO THE EDITOR

Continued Exploration of Bevacizumab in Breast Cancer

TO THE EDITORS:

We appreciate the opportunity to discuss the need for continued exploration of bevacizumab in breast cancer. As aptly noted by Drs. Ziogas and Roukos, the routine use of bevacizumab should be discouraged in the adjuvant or neoadjuvant setting in breast cancer; however, carefully designed research studies should be encouraged to further understand the indications for the optimal use of the anti-angiogenic agents. In our published paper, we reported the response of 16 HER-2-negative patients who received bevacizumab with chemotherapy and compared the results with 20 patients who did not receive bevacizumab. Although the main focus of that work was the evaluation of the imaging findings, the pathologic response between these two groups was also reported.

The perceived lack of benefit seen with use of bevacizumab is the result of many reasons, in addition to the ones discussed by Drs. Ziogas and Roukos. In fact, the reported patients in this study were a subset of a larger number of patients treated at Chao Family Comprehensive Cancer Center since 2003 (listed in http://clinicaltrials.gov). The pathologic complete response (pCR) rate was high despite inclusion of patients with inflammatory and metastatic breast cancer, which might be attributed to application of the following chemotherapy paradigms. First, we used optimal scheduling of doxorubicin and cyclophosphamide as induction therapy. Second, if a 50% reduction in the tumor size was not attained after two cycles of doxorubicin and cyclophosphamide, patients were switched to the second-line regimen earlier. Third, because weekly paclitaxel has an antiangiogenic effect, weekly low-dose paclitaxel is considered the best way of administration, and it has been found to have better efficacy than once-every-3-weeks paclitaxel scheduling.[1–5] Fourth, we used carboplatin with weekly paclitaxel, which may specifically be important in triple-negative breast cancer.[4]

In our article, we only analyzed the subset of patients who had completed magnetic resonance imaging (MRI) study. Although the response in 16 patients (17 lesions) who received bevacizumab was slightly inferior (5 of 17, 29%) to patients who did not receive bevacizumab (8 of 20, 40%), as a result of the small subject number and nonrandomized study design, this result did not provide sufficient supporting evidence to discourage the use of bevacizumab, and more research is definitely needed. Importantly, HER-2-negative breast cancer comprises heterogeneous subsets of breast cancer that include luminal A, luminal B, triple-negative nonbasal, triple-negative basal, and *BRCA*-associated breast cancers, and all these factors may affect the reported pCR rate.

We also agree with the other limitations described by Drs. Ziogas and Roukos. We are following all patients enrolled onto our previous and current treatment studies to obtain the long-term disease-free and overall survival data. Regarding the predicted power of pCR, this issue is an important research topic in the field of oncology, and more data should be forthcoming. As the association between residual disease burden and patient's prognosis becomes better established and more widely accepted, dichotomizing patients into pCR versus non-pCR should not be the only way to predict prognosis.[6] As we showed in our article, MRI is not sensitive to detect minimal residual disease presenting as scattered cells or cell clusters. If it is further proven that patients with minimal residual disease (small residual cancer burden) have comparable prognosis as those achieving pCR, the MRI findings may play an important role in management of these patients, despite this modality's limited sensitivity in detecting such residual diseases.

Further exploration of the indication for use of bevacizumab is a laudable goal, and the Southwest Oncology Group and Eastern Cooperative Oncology Group have proposed large, randomized neoadjuvant trials that will test some of the above-discussed paradigms, which include dose-dense doxorubicin and cyclophosphamide sequenced to metronomic (weekly) paclitaxel, with or without carboplatin and with or without bevacizumab. Therefore, although we strongly agree with Drs. Ziogas and Roukos that caution should be used in the routine use of bevacizumab in treatment protocols, we think that more research studies that use appropriately designed protocols approved by an internal review board, with patient's written informed consent, should be encouraged. Furthermore, we think that imaging can play an important role, particularly in the neoadjuvant setting, and indeed, incorporating imaging into clinical cancer treatment trials is the current trend. The role of imaging in guiding adjustment of the optimal treatment protocol, as well as in planning of the

optimal surgical procedure after completing treatment, should be investigated. The traditional biomarkers used for management of breast cancer are molecular biomarkers. The concept of using imaging findings as biomarkers is evolving, and it is particularly suitable for management of patients receiving neoadjuvant chemotherapy. Last, as discussed by Drs. Ziogas and Roukos, there is a great need for a better understanding of the molecular mechanisms and genotype-phenotype relationships so that personalized decisions about the use bevacizumab or other targeted agents may be made.

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Published Online: 21 November 2009

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