Research Highlight

Bevacizumab: Where do we go from here in breast cancer?

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Bevacizumab is a monoclonal antibody against circulating vascular endothelial growth factor A, which received accelerated FDA approval in 2008 for first line treatment of HER2-negative metastatic breast cancer. The initial approval was based on studies suggesting a progression-free survival and not overall survival. This observation served as the basis for looking into the use of bevacizumab as an adjunct to neoadjuvant chemotherapy in the treatment of HER2-negative breast cancer.

In the January 2012 issue of the NEJM Bear *et al.* reported the results of the NSABP B-40 trial in which 1,206 patients with clinical T1c-T3, N0-N2, M0 HER2-negative tumors were randomized to receive one of three neoadjuvant chemotherapy regimens (regimen 1: docetaxel, 100 mg/m^2 on day 1; regimen 2: docetaxel, 75 mg/m^2 on day one plus capecitabine, 825 mg/m^2 on days 1 and 14; regimen 3: docetaxel, 75 mg/m^2 on day one plus gemcitabine, 1,000 mg/m^2 on days 1 and 8; all given for four cycles, followed by 4 cycles of doxorubicin-cyclophosphamide) (1). Within each treatment arm patients were further randomized to receive or not to receive bevacizumab, 15 mg/m^2, for the first 6 cycles of chemotherapy. The primary end-point was pathologic complete response in the breast; the secondary end-points were clinical complete response after completion of docetaxel portion of chemotherapy and at the completion of the entire neoadjuvant therapy regimen, pathologic complete response in the breast and the lymph nodes and incidence of the New York Heart Association (NYHA) class III or IV congestive heart failure and of other cardiac events.

The study demonstrated that the addition of neither capecitabine nor gemcitabine contributed to an improvement of the pathologic complete response rate (29.7% and 31.8%, respectively, *vs.* 32.7%; P=0.69). However, the addition of bevacizumab significantly increased the rate of pathologic complete response in the breast alone (28.2% *vs.* 34.5%, P=0.02). Although statistically significant this benefit was modest and not seen when the breast and axilla response were combined. This came at the cost of increased toxic side effects. In the same issue a companion article by von Minckwitz et al. reporting for the GeparQuinto trial showed benefit in the hormone-receptor negative population as opposed to Bear *et al.*, reporting its greatest benefit in the hormone receptor positive cancers (2). The role of bevacizumab in the treatment of breast cancer remains to be fully elucidated. There may be a subset of patients who would benefit from bevacizumab in the metastatic, neoadjuvant or adjuvant setting. Unfortunately current data do not give guidance to the group that may benefit the most.

The results from the GeparQuinto study were initially presented at the 33rd San Antonio Breast Cancer Symposium in December of 2010 and at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in June 2011, while the NSABP B-40 trial results were presented I at the June 2011 ASCO meeting as well. These studies were subsequently published in January of 2012 in the NEJM, following a crucial recommendation issued by the Food and Drug Administration (FDA) on November 18th 2011 to revoke the agency's previous accelerated approval of bevacizumab for the treatment

of breast cancer. The basis for this decision stems from the toxicity data on the drug in the setting of metastatic breast cancer, which demonstrate that its risks, some of which are potentially life-threatening, are outweighed the drug's limited beneficial impact on disease-free and overall survival. While the results of the two studies suggest that bevacizumab may have a role in the treatment of HER2-negative breast cancer in the neoadjuvant setting, these data are unlikely to find clinical application in the US at this time due to the afore-mentioned decision by the FDA, but it remains to be seen with maturation of data from these trials and others that are nearing completion will result in any appeals to the FDA to reverse its decision to revoke bevacizumab's approval.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2012.03.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

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