Research Highlight

Neoadjuvant bevacizumab and chemotherapy in breast cancer

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Bevacizumab (Avastin, Roche-Genentech) is a humanized monoclonal antibody targeting all isoforms of the vascular endothelial growth factor A (VEGF-A), an important regulator of angiogenesis. It stimulates endothelial cell proliferation/migration as well as induces vascular leakage or vasodilatation, which are essential in a variety of physiological and pathological conditions (1). It has been found that VEGF-A expression is upregulated in various human tumors. Over the past decade, bevacizumab has been incorporated into chemotherapy for the treatment of cancer patients with advanced diseases including colorectal cancer, non-squamous non-small cell lung cancer, renal cell carcinoma and glioblastoma.

Recently, two randomized phase III clinical trials evaluated neoadjuvant bevacizumab plus chemotherapy for early and locally advanced HER2-negative breast cancer - one is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-40 trial and the other is the GeparQuinto (GBG44) trial (2,3). The primary endpoint of both studies was to compare pathological complete response (pCR) rate, a surrogate endpoint for neoadjuvant therapy efficacy, of neoadjuvant chemotherapy with or without bevacizumab in patients with HER2-negative primary breast cancer. Patients were eligible if they had a tumor stage T1c to T3, nodal stage N0 to N2a and no distant metastases specified in the NSABP B-40 trial or the criteria as NSABP B-40 plus stage 4a to 4d and nodal stage N3 in the GeparQuinto trial. The addition of bevacizumab to chemotherapy significantly and moderately increases pCRrate (34.5% *vs*. 28.2%, P=0.02) in the breast by the NSABP B-40, and in the breast and nodes (18.4% *vs*. 14.9%, P=0.04) by the GeparQuinto. Additionally, pCR rate was not significantly increased by adding capecitabine or gemcitabine to docetaxel compared to docetaxel monotherapy in NSABP B40 study. Both study results were published in the Journal of *New England Journal of Medicine* in the January 26, 2012 issue amid the controversy or debate over bevacizumab in the treatment of HER2-negative locally recurrent or metastatic breast cancer.

In November 2011, based on the lack of survival benefit or improvement on the quality of life, and small improvement in progression-free survival (less than three months) by adding bevacizumab to capecitabine or a taxane/an anthracycline from the two double-blind randomized phase III studies (AVADO and RIBBON-1) in HER2-negative metastatic breast cancer (4,5), the Food and Drug Administration (FDA) revoked the approval of bevacizumab in combination with paclitaxel as first-line treatment for metastatic breast cancer in the United States (http://1.usa.gov/v3KYnY). The FDA initially granted an accelerated approval for bevacizumab in metastatic breast cancer in February 2008 based on the Eastern Cooperative Oncology Group (ECOG) 2100 trial results, in which the addition of bevacizumab to weekly paclitaxel chemotherapy significantly improved progression-free survival (median, 11.8 *vs*. 5.9 months) and nearly doubled objective response rate (6). However, it is yet to be confirmed whether the choice of chemotherapy agents or regimens for use in combination with bevacizumab could be more or less effective or has an impact on the magnitude of improvement of progression-free survival.

In both neoadjuvant trials, bevacizumab plus chemotherapy versus chemotherapy alone increased grade 3/4 adverse events that have been associated with bevacizumab such as hypertension, proteinuria, headache, and/or left ventricular dysfunction or aggregating the toxicities of chemotherapy agents, for example, neutropenia, mucositis, hand-foot syndrome or infection similar largely to the reports from previous bevacizumab trials (4-6). It was the concerns on its safety profile that has partially contributed to the decision of withdrawal of the drug for metastatic breast cancer (http://1.usa.gov/v3KYnY). Interestingly, the

surgical complications of only 2% and 14.7% in NSABP B-40 and GeparQinto, respectively, were much lower than what would have predicted. In our own study using neoadjuvant bevacizumab in 21 patients with inflammatory and locally advanced breast cancer, we experienced a 24% complication rate in all patients and 39% complication rate in patients that underwent surgery (7). This is similar to a 43% surgical complication rate reported by Golshan *et al*. in another small neoadjuvant trial administering cisplatin in combination with bevacizumab to 51 patients (8). The type of events that were considered "complications" was not elaborated in detail in the two Phase III studies. Nonetheless, this is a toxicity that will need to be followed as the use of bevacizumab increases in the neoadjuvant setting.

In the subset analyses, the divergent occurs on the subgroups of patients who benefited from the combination treatment. The addition of bevacizumab significantly increases pCR rate in patients with hormone receptor-positive tumors by NSABP B-40 whereas in those with the triple-negative subset by GeparQuinto (2,3). The discrepancy itself may suggest that hormone receptors might not be the critical factors for bevacizumab efficacy or benefit in HER2-negative population in the neoadjuvant setting. We anticipate that both trials will provide opportunities to delineate the molecular markers, which have emerged from single arm bevacizumab chemotherapy clinical trials that are associated with overall survival (9), using the tissues collected before the initiation of treatment. In addition, the biopsies or specimens collected on therapy or after surgery following neoadjuvant treatment could facilitate the identification of the biomarkers of resistance. It would be the identification of subset patients who maximally benefit from the administration of bevacizumab that holds the key for successful use of this drug. At this point, the data for overall survival is premature and it is matter of time before we know whether pCR will translate into an increase in overall survival.

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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.2012.03.04). 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

1. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr Rev 1997;18:4-25.
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. 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.
4. Miles DW, Chan A, Dirix LY, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010;28:3239-47.
5. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011;29:1252-60.
6. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666-76.
7. Wedam SB, Low JA, Yang SX, et al. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol 2006;24:769-77.
8. Golshan M, Garber JE, Gelman R, et al. Does neoadjuvant bevacizumab increase surgical complications in breast surgery? Ann Surg Oncol 2011;18:733-7.
9. Yang SX, Steinberg SM, Nguyen D, et al. p53, HER2 and tumor cell apoptosis correlate with clinical outcome after neoadjuvant bevacizumab plus chemotherapy in breast cancer. Int J Oncol 2011;38:1445-52.

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