Bevacizumab in Neoadjuvant Chemotherapy Increases the Pathological Complete Response Rate in Patients With Triple-Negative Breast Cancer

A recent study demonstrated increased pathological complete response (pCR) rates when bevacizumab is added to the neoadjuvant chemotherapy regimen in patients with triple-negative breast cancer (TNBC) (Ann Oncol. 2013;24:2978-2984). This research is part of the multicenter GeparQuinto study, conducted by investigators from the German Breast Group. TNBC is defined as breast cancer that is negative for estrogen and progesterone receptors, as well as human epidermal growth factor receptor 2 (HER2). Better ways to treat TNBC are needed because it confers a high risk of recurrence and mortality.

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, has a controversial role in the treatment of breast cancer. It was approved by the US Food and Drug Administration for the treatment of patients with metastatic breast cancer in 2008 under an accelerated plan that allows for approval based on data that are not complete enough for full approval, but approval was revoked in 2011 when further studies demonstrated no overall survival or quality-of-life benefits.

However, bevacizumab has extended progression-free survival across multiple studies when added to chemotherapy for metastatic disease. In one of those studies, a subset analysis demonstrated improved overall survival in patients with TNBC (Breast Cancer Res Treat. 2012;133:1067-1075). The current study evaluates the potential role of bevacizumab in the neoadjuvant treatment of patients with TNBC.

The initial report of this trial, the GeparQuinto study, was published in 2012 (N Engl J Med. 2012;366:299-309). In that study, the addition of bevacizumab was found to increase the pCR rate in patients with HER2-negative early breast cancer. The primary objective was to compare the pCR rates after neoadjuvant chemotherapy with or without bevacizumab in a predefined subset of patients with TNBC. pCR is defined as the lack of residual disease in the breast or lymph nodes at the time of surgery.

Study Details and Results

The current report addressed specifically those 663 patients from the GeparQuinto study with central confirmation of TNBC. All patients received neoadjuvant epirubicin and cyclophosphamide for 4 cycles, followed by 4 cycles of docetaxel. Patients were randomized to 8 cycles of bevacizumab at a dose of 15 mg/kg every 3 weeks along with the chemotherapy or chemotherapy alone.

Of the patients who received bevacizumab, 39.3% achieved pCR, versus 27.9% of patients who received chemotherapy alone (P = .003). When examining pCR rates in the breast alone (not including the lymph nodes), the difference was 41.8% versus 30.9% (P = .004) in favor of bevacizumab. In an analysis adjusted for age, tumor and lymph node classification, and histological tumor type and grade, the pCR rate remained increased with the addition of bevacizumab (overall risk, 1.73; P = .002). Lower tumor stage and grade 3 tumors were found to be independent predictors of higher pCR rates. The rate of breast-conserving surgery did not differ between groups. Toxicity analysis demonstrated significant increases in the incidence of febrile neutropenia, infections, mucositis, and hand-foot syndrome with the addition of bevacizumab.

It is important to note that pCR is increasingly being accepted as a surrogate marker for recurrence-free survival, because recent data have shown a strong correlation. In fact, the US Food and Drug Administration has said in draft guidance that it will accept pCR as a surrogate marker in the approval of drugs to treat breast cancer.

A simplified diagram of vascular endothelial growth factor (VEGF) pathways.
Conflicting Reports?
The results of a different study, Cancer and Leukemia Group B (CALGB) 40603, were presented as an abstract at the 2013 San Antonio Breast Cancer Symposium held last December in Texas (Abstract S5-01). In that study, 454 patients with TNBC were randomized to receive standard neoadjuvant chemotherapy, chemotherapy plus either carboplatin or bevacizumab, or both. In the breast alone, the addition of bevacizumab significantly increased pCR rates from 48% to 59% ($P = .0089$). In addition, the addition of bevacizumab increased the rate of pCR in the breast and axilla from 44% to 52%, but this difference was not found to be statistically significant ($P = .057$). The addition of carboplatin conferred significant increases in both parameters. Although patients who received both carboplatin and bevacizumab had the highest pCR rates, the combination did not demonstrate any synergy. Toxicity was found to be increased in the patients treated with bevacizumab with more grade 3 hypertension, infections, and postsurgical complications reported, with a slight increase in thrombosis and bleeding problems. Because of the increased toxicities, the authors and discussants did not believe the risk-benefit ratio of adding bevacizumab was favorable.

Clinical Significance Questioned
“The differences between results from GeparQuinto and CALGB 40603 are relatively modest; the difference in pCR breast/axilla rates in [CALGB] 40603 between the groups with or without bevacizumab just missed statistical significance ($P = .057$),” says William Sikov, MD, presenter of the CALGB 40603 study and associate professor of medicine at the Warren Alpert Medical School of Brown University in Providence, Rhode Island. “The bigger questions are whether the magnitude of the differences between pCR rates is clinically significant, even if statistically significant, and whether the increase in pCR rates will translate into improvements in survival endpoints, which are more important than pCR.”

Without long-term survival rate data, researchers question the treatment benefit of adding bevacizumab to neoadjuvant chemotherapy for patients with TNBC.

“In general, there is clear evidence now that bevacizumab can improve the pCR rate when added to neoadjuvant chemotherapy in patients with TNBC,” says Gunter von Minckowitz, MD, PhD, chairman of the German Breast Group, professor at the University of Frankfurt in Germany, and principle investigator of the GeparQuinto study. “However, as long as no survival data are available, we cannot promote this treatment, taking into account also the negative results from the BEATRICE study that added bevacizumab to chemotherapy in the adjuvant setting,” he adds (Lancet Oncol. 2013;14:933-942). “However, the neoadjuvant efficacy might differ from adjuvant as the tumor is still in place, so that inhibition of angiogenesis might be more relevant.”

“Given the uncertainty as to the long-term benefit of the higher pCR rates seen with bevacizumab and the associated toxicities, I do not think its use in the neoadjuvant setting is warranted unless survival results from CALGB 40603 and GeparQuinto, though underpowered for this endpoint, show a benefit, or correlative studies identify a subset of patients who get a much larger response benefit from bevacizumab,” says Dr. Sikov.

“These analyses are ongoing, and some of the results will be available this year,” says Dr. Sikov. “Meaningful recurrence-free survival results are probably no more than 2 to 3 years off, since we expect most patients who recur will do so within 3 to 4 years from surgery given the aggressive biology of TNBC.”

Likewise, Dr. von Minckowitz added that he hopes to report survival data from the GeparQuinto study this year.

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