Editorial

The addition of bevacizumab to neoadjuvant chemotherapy in HER2-negative inflammatory breast cancer, more not necessarily better

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Inflammatory breast cancer (IBC) is rare and aggressive form of invasive ductal carcinoma with a 5-year survival rate of only 40% as compared to 85% survival rate in other types of breast cancer patients (1,2). The poor prognosis of IBC is probably due to its high metastatic potential (3). The standard systemic management includes chemotherapy, in addition to anti-hormone and/or anti-human epidermal growth factor receptor-2 (anti-HER2) therapy, depending on the expression of the relevant receptors (3-8). Angiogenesis is known to be required for proliferation of tumor cell (9,10), the activity of which is determined by the extent of micro vessel density (MVD), which may serve as a surrogate of aggressiveness of the breast cancer (9). The most abundant angiogenic polypeptide expressed by primary breast cancers is vascular endothelial growth factor (VEGF) and is associated with increased angiogenesis (11,12). Besides angiogenesis, VEGF is also associated with endothelial and tumor cell growth and motility, as well as, blood vessel permeability (13).

Increased VEGF expression has a direct inhibitory effect on angiogenic parameters like negative response to tamoxifen or chemotherapy in patients with advanced breast cancer (14-16). Bevacizumab is a humanized monoclonal antibody directed against circulating VEGF, where VEGF is known angiogenesis stimulator (17). Bevacizumab blocks this ligand from interacting with its receptor (18).

BEVERLY-1 is a multi-institutional, phase 2, single arm clinical trial (15) aimed to evaluate the benefit of adding of bevacizumab to neoadjuvant chemotherapy and thereafter, postoperatively, as maintenance therapy of patients with HER2-negative IBC. Inclusion criteria of patients on study consisted of untreated, pathologically confirmed, unilateral, HER2-negative (evaluated by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH), or chromogenic in situ hybridization (CISH) non-metastatic, IBC. The main exclusion criteria included absence of history of other cancer(s) (other than curatively treated squamous and basal cell carcinoma of the skin, in-situ carcinoma of the cervix) within the 5 years before study entry, in-situ contralateral breast cancer, non-IBC, metastatic IBC, HER2-positive tumor, previous treatment with chemotherapy, radiotherapy, or hormone therapy for the current IBC, and pregnancy or breastfeeding. Patients received, in addition to bevacizumab, 15 mg/kg, four cycles of FEC (fluorouracil, 500 mg/m^2, epirubicin, 100 mg/m^2, cyclophosphamide (500 mg/m^2), followed by four cycles of docetaxel, 100 mg/m^2, given every 3 weeks. Patients received adjuvant radiotherapy and hormone therapy. Bevacizumab (15 mg/kg) was restarted during (concomitant) or after (sequential) radiotherapy, as soon as wound healing was complete (2–4 weeks after surgery), intravenously on day 1 of each cycle for ten 3-week cycles. Sataloff classification (16) was used to determine the primary endpoint, which was described as the proportion of patients achieving a pathological complete response in breast and axillary lymph nodes after neoadjuvant treatment. Of the 100 patients enrolled in the study, only 19 [19% (95% CI, 12–28%); P=0.16] achieved a pathological complete responses. The authors concluded that the addition of bevacizumab to neoadjuvant and adjuvant chemotherapy did

not provide clinical benefit to patients with non-metastatic HER2-negative IBC (15).

Two published trials reported of pCR rates of 32% and 20.1% after anthracycline-based dose dense (19,20), showing no demonstrable advantage to its addition. On the other hand, two randomized phase 3 clinical trials, NSABP-B40 (21), and ARTemis (22) and a randomized phase 2 trial, CALGB 40603 (23) examined the addition of bevacizumab to neoadjuvant anthracycline-taxane-based chemotherapy in HER2-negative non-IBC, demonstrated significant increase of patients attaining a pathological complete response.

In NSABP-B40 trial (21), overall survivals were increased, with a significant reduction in the incidence of distant metastases. The ARTemis (22) and CALGB 4060323 (23) trials did not include disease-free survival (DFS) or overall survival as end points. Interestingly, the DFS result in current study (57% at 3 years), albeit short follow up, is superior to those reported in Pegase 02 with high-dose chemotherapy (44%) (19) and similar to Pegase 07 (60%), where effect of docetaxel–fluorouracil without bevacizumab was studied (20).

The lack of added efficacy from adding bevacizumab, according to the authors, may be due to reduced chemo sensitivity compared with early-stage non-IBC (24). More importantly, angiogenesis, lymph angiogenesis, and vasculogenesis makes blockade of VEGF by bevacizumab less efficient in IBC than in non-IBC, and hence were the major contributor for the effect (22). The non-consistent reported results could be because of the heterogeneity in chemotherapy regimens and numbers of bevacizumab cycles used, or how was the pCR defined.

Bevacizumab induces tissue hypoxia which may inherently result in increased chemo resistance of breast cancer stem cells (21), in addition to an accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis (25). It was demonstrated that angiogenesis inhibition in mice can lead to opposing effects on tumor growth and metastasis depending on tumor stage and treatment duration. The benefits of VEGF-targeted agents in the treatment of late-stage cancers can be transitory, resulting in eventual drug resistance, tumor growth and/or regrowth, and rapid vascular recovery when therapy is stopped (25).

As a secondary outcome, the study did not find any prognostic role of the circulating endothelial cell status in pathological complete response, disease free survival, or overall survival. Also, there was no association of the decrease in circulating tumor cell counts during the first neoadjuvant treatment cycle with pathological response, whereas it was associated with reduced 3-year disease-free survival (15).

The authors concluded that the backbone treatment of the HER2 negative IBC patients is taxane-anthracycline chemotherapy in the neoadjuvant setting, and adjuvant hormone therapy in case of hormone receptor-positive disease: bevacizumab added no benefit, however. The arguments for the added bevacizumab continue to be unsettled. We suggest that a meta-analysis of all trials addressing this issue may give a better idea of where to place bevacizumab in the neoadjuvant chemotherapy paradigm. In addition, additional DFS and OS survival data of the published trials, when made available, may also help to better define its role.

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Footnote

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