



The combination of bevacizumab with chemotherapy is more beneficial in the metastatic setting rather than in the adjuvant setting for the treatment of HER2-negative breast cancer—a commentary on the E5103 randomized phase III clinical study

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The randomized phase III, double-blind, clinical trial (E5103) enrolled 4,995 patients with human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer and evaluated the efficacy and the safety of humanized monoclonal antibody bevacizumab targeting vascular endothelial growth factor (VEGF) in adjuvant chemotherapeutic setting (1). The rationale of the study was based on the results from the metastatic setting where the combination of bevacizumab with chemotherapy has shown a significant improvement of progression free survival (2-7) and a pathologic complete response in the neoadjuvant setting (8-12). The E5103 aimed to improve patients' survival outcomes. Patients were randomized in three arms: placebo with doxorubicine and cyclophosphamide followed by paclitaxel (arm A); same chemotherapeutic combination plus bevacizumab (arm B and C); in particular, patients in arm C continued bevacizumab for almost one year, together with radiation and hormonal therapy. Invasive disease-free survival (IDFS) was the primary end point. The 5-year IDFS rates were 77% (95% CI, 71% to 81%) in arm A, 76% (95% CI, 72% to 80%) in arm B, and 80% (95% CI, 77% to 83%) in arm C. The differences in IDFS between the 3 arms were not statistically significant. The overall survival (OS) at 5 years were 90% (95% CI, 87% to 92%), 86% (95% CI, 83% to 88%) and 90% (95% CI, 88% to 92%) in arms A, B and C, respectively. On the same

line of the IDFS differences, the differences in OS were not statistically significant between the three groups (1).

The hypothesis lying behind these negative results obtained from this clinical trial are different in our opinion. First, there was a substantial early discontinuation of bevacizumab: about 24% of patients in arm B and 55% in arm C interrupted the treatment due to the adverse events (AEs). The AEs across arms included myelosuppression and neuropathy. Grade ≥ 3 hypertension was the most commonly frequent in experimental arms, but others bevacizumab-related AEs were similar reported in all arms.

Secondly, the discontinuation of therapy due to the AEs provoked by the administration of adjuvant bevacizumab was also responsible for the interruption in the provision of chemotherapy. The pre-planned additional chemotherapeutic regimens for patients enrolled into arms B and C could have been beneficial in improving their IDFS and OS. Thus, the results could have been much different if bevacizumab did not lead to AEs-caused interruption of all the successive treatment schedules of arms B and C. The 40% of patients in arm C did not proceed to bevacizumab monotherapy mostly due to the withdrawn of the consent or due to the toxicity.

Third, the absence of predictive biomarkers, fourth, it should be considered that there are multiple mechanisms of resistance to anti-VEGF therapy such as the induction of

alternative angiogenic pathways (Fibroblast Growth Factor, Hepatocyte Growth Factor c/Met, Platelet-Derived Growth Factor, Epidermal Growth Factor, Insulin-Like Growth Factor), hypoxia-mediated increases, cancer stem cells that can grow without the need of the mitogenic factors present in serum (13), autophagy and compensatory recruitment of vascular progenitors.

Similar results were previously obtained from the BEATRICE clinical trial, a randomized, open-label, phase III trial with 1,290 Triple Negative Breast Cancer (TNBC) patients testing the chemotherapy either alone or with bevacizumab (5 mg/kg every week for 1 year). The primary endpoint was IDFS (14) which was not met: there was no difference between groups in IDFS (HR 0.87; with a small difference in 3-year IDFS and 5-year IDFS rates (14,15). Moreover, after 56 months leading to 293 patients been deceased the measured OS was not statistically different between the two groups (HR 0.93, 95% CI, 0.74–1.17; P=0.52). All the other secondary endpoints were in favor of the bevacizumab arm, but none of them was statistically significant (14).

In adjuvant setting the target of treatment should be eventually the micro-metastases present in the body but they are hard-to-be-treated using anti-angiogenic treatments aiming to target blood vessels. Moreover, the potential bevacizumab-resistance could have been also inferred by cancer stem cells capable of proliferating without the need for blood supply or because of other angiogenic pathways.

In conclusion, using treatments capable of blocking the pathways responsible for resistance to bevacizumab along their combination of bevacizumab and not with the use of bevacizumab alone could be interesting to be pursued in combination also with chemotherapy in the adjuvant setting of HER2-negative breast cancer.

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