We declare no competing interests.

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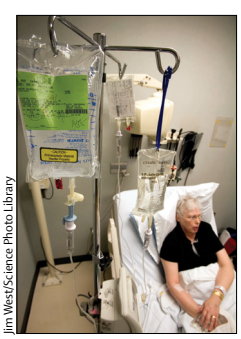
Bevacizumab: the phoenix of breast oncology?



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Bevacizumab is a monoclonal antibody that inhibits tumour neoangiogenesis mediated by VEGF. In a meta-analysis that included 2447 patients with breast cancer treated in a first-line setting, bevacizumab slightly improved progression-free survival (HR 0·64, 95% CI 0·57–0·71; median 9·2 months *vs* 6·7 months) and did not improve overall survival (HR 0·97, 95% CI 0·86–1·08; 26·7 months *vs* 26·4 months).[1] Guidelines recommend this drug as an option only in selected cases because of the slight improvement in progression-free survival, lack of benefit in overall survival, high cost, lack of predictive biomarkers, and associated toxicities.[2] More recently, a phase 3 randomised trial reported that bevacizumab did not improve outcome as adjuvant treatment in patients with triple-negative breast cancer.[3] It is important to emphasise that this trial was done in patients with intermediate risk of relapse, and the effect of bevacizumab in high-risk patients is still unknown. Overall, although the drug is still widely used in several countries, the enthusiasm associated with bevacizumab has dramatically decreased, and some countries have either restricted or stopped its use.

In *The Lancet Oncology*, Helena Earl and colleagues[4] report pathological complete response results of a phase 3 randomised trial assessing the efficacy of bevacizumab in the neoadjuvant setting. A significantly greater proportion of patients treated with bevacizumab and chemotherapy achieved a pathological complete response (22% [95% CI 18–27]) compared with those treated with chemotherapy alone (17% [13–21]). The magnitude of improvement was numerically more pronounced in patients with oestrogen receptor (ER) negative (45% [95% CI 36–55] *vs* 31% [23–40]) or ER poor (51% [34–68] *vs* 30% [16–47]) breast cancer, as opposed to those with ER strongly positive breast cancer (6% [3–10] *vs* 7% [4–11]).

The GeparQuinto, NSABP B-40, and CALGB 40603 randomised trials have also assessed the efficacy of bevacizumab in the neoadjuvant setting.[5-7] All three trials[5-7] reported that adding bevacizumab to chemotherapy could improve pathological complete response. Nevertheless, they did not report consistent data about which molecular subclass could derive greater benefit. GeparQuinto and CALGB 40603 reported high benefit in triple-negative breast cancer, whereas NSABP B-40 reported higher benefit in ER-positive disease. Trials in the metastatic setting failed to show that patients with triple-negative breast cancer derived more benefit from bevacizumab than those with other subtypes. Overall, although they diverge on subgroup analyses, the four trials report consistent data that bevacizumab could increase pathological complete response in patients with early breast cancer.

Although consistent, these data should not lead to the use of bevacizumab in early breast cancer for several reasons. First, a randomised trial[3] in the adjuvant setting, although done in the earlier stages of breast cancer, was reported to be negative. Second, the improvement in pathological complete response was not dramatic in populations in which such response was assessed as a primary outcome. Nevertheless, this wave of randomised trials in the neoadjuvant setting, pending cooperation between the groups and support

from funding agencies, will certainly open a new era for the development of bevacizumab in breast cancer.

First, these randomised trials will enable a meta-analysis to be done. A meta-analysis will allow better understanding about which population derives more benefit, which chemotherapy backbone is the most appropriate, and will assess the effect of bevacizumab on outcome (disease-free survival and overall survival) in a large population of patients presenting with high-risk breast cancers. To what extent an improvement in pathological complete response translates into disease-free survival and overall survival benefit is still controversial in breast cancer, and this meta-analysis, based on a large number of patients, will certainly help. Second, neoadjuvant studies could allow the development of a molecular predictor for the efficacy of bevacizumab. The predictor could be cross-validated in different trials because four studies are now available. Several molecular predictors have already been proposed, including vascular cell adhesion molecule 1, intercellular adhesion molecule 1, E-selectin, and circulating VEGFR-2.[8] Because most trials were done in a metastatic setting, no opportunity existed until now to test tissue-based biomarkers in samples obtained at baseline before therapy. Finally, neoadjuvant studies, where pre-treatment and post-treatment samples are available, could allow the discovery of new mechanisms of action for bevacizumab. For example, bevacizumab has been reported to modulate the immune system through dendritic cells and regulatory T-cell functions, and could facilitate T-cell homing.[9] If molecular analyses from neoadjuvant studies confirm an effect of bevacizumab on the immune system, they could generate a rationale for triple combination therapy of immunogenic chemotherapy, anti-PD1 agents, and bevacizumab.

Overall, the study by Earl and colleagues,[4] consistent with previous trials, suggests that bevacizumab could improve pathological complete response in patients with breast cancer. These four trials could constitute the starting point of a new era for bevacizumab in breast oncology and could help to define which patients are more likely to benefit from bevacizumab, and which drug should optimally be combined with it.

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Parenthood in female survivors of Hodgkin's lymphoma

In *The Lancet Oncology*, Jurgen Brämswig and colleagues[1] report pregnancy outcomes in 467 female long-term survivors of Hodgkin's lymphoma who were younger than 18 years at diagnosis and treated in one of five concurrent clinical trials in Germany and Austria between 1978 and 1995. The investigators are to be congratulated for this important contribution to the understanding of long-term pregnancy outcomes in female survivors of Hodgkin's lymphoma. They have shown that the chance of these patients becoming a parent is similar to that in the female German population aged 16–39 years, and not significantly affected by potentially gonadotoxic

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