Viewpoint

Anti-VEGF therapy as adjuvant therapy: clouds on the horizon?

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Abstract

Anti-angiogenic therapies have demonstrated their value in the setting of advanced cancer, and are being explored for use in micrometastatic disease. Recent preclinical studies suggest that adjuvant anti-vascular endothelial growth factor (VEGF) therapies may increase the risk of metastasis. How concerning are these preclinical studies, and should they affect our willingness to explore anti-VEGF therapy in the adjuvant setting?

Background

The anti-vascular endothelial growth factor (anti-VEGF) therapy bevacizumab was approved for metastatic breast cancer based upon two randomized controlled trials, E2100 and AVADO, that randomized women to receive taxane therapy alone or in combination with bevacizumab for HER2-negative metastatic disease [1,2]. Both trials demonstrated a significant improvement in progression-free survival; neither demonstrated an improvement in overall survival, though both were poorly powered. Other phase II trials suggest benefit from the combination of anti-VEGF therapies with anti-HER2 therapies [3,4].

Based upon these results, adjuvant trials have begun in HER2-negative and HER2-positive populations. E5103 randomizes women with HER2-negative disease to receive either chemotherapy (ACT - doxorubicin, cyclophosphamide, and paclitaxel) alone or in combination with bevacizumab (administered either concurrently with chemotherapy or for a year). BETH randomizes HER2-positive patients to receive either a standard chemotherapy/trastuzumab combination or the same with bevacizumab. Both are large, well-powered trials with primary disease-free survival endpoints and secondary overall survival endpoints.

The Article

It is against this backdrop that the work of Ebos and colleagues [5] should be considered. They examined the small molecule receptor tyrosine kinase inhibitor sunitinib as adjuvant therapy in a mouse human tumor xenograft model of breast cancer, 231/LM2-4LUC+. They demonstrated that short-term (7 day) administration of sunitinib, either before or after tail vein inoculation, accelerated metastasis and impaired survival. Similar results were obtained in a 231/LM2-4LUC+ spontaneous model of metastasis. A human melanoma xenograft model also gave generally similar results, though a murine melanoma syngeneic model revealed what were said to be 'biphasic effects, with about half of the mice progressing with accelerated metastasis and the remainder showing a prolongation in survival.' Sustained sunitinib therapy, in contrast to short-term therapy, decreased primary tumor growth without improving metastasis-related survival.

The same authors, in previous work, have demonstrated that treatment with anti-VEGF agents is associated with host-related increases in several cytokines, including osteopontin, granulocyte colony-stimulating factor, and SDF1a [6]. The current work does not address the role of drug-induced cytokine production, nor the possibility of rebound re-growth of blood vessels documented by other investigators in the laboratory [7] or the clinic [8] following cessation of anti-VEGF agents.

The Viewpoint

These provocative findings [5] (and similar work by Pàez-Ribes and colleagues [9]) suggest that in trying to do good with adjuvant anti-VEGF therapy we might create the great harm of increasing distant metastatic disease. How concerned should we be?

All preclinical model systems have limitations and should be viewed with caution. Model systems such as the 231/LM2-4LUC+ model employed by Ebos and colleagues are beloved by investigators because they reproducibly metastasize in quicksilver fashion [5]. The clinic is different: patients (and their tumors) are heterogenous, metastasize to multiple organs, and develop overt metastasis over years. In addition, anti-VEGF agents demonstrate benefits across multiple cancer types. The macrometastatic setting has been

VEGF = vascular endothelial growth factor.

our best predictor of success in micrometastatic disease. While nothing is impossible, it seems unlikely that benefits seen in advanced disease will suffer a complete reversal of fortune in the curative setting.

These findings do raise critical issues regarding adjuvant anti-VEGF therapy. While unlikely to cause decrements to an entire population, it is possible that subgroups will experience inferior outcomes. In the study by Pàez-Ribes and colleagues [9], differences in invasiveness were seen in RIP1-Tag2/Cre;Vegf-Afl/fl mice (b-VEGF-KO) when compared to b-VEGF-WT. These findings demonstrate that inherited (not mutational) variability is important in the angiogenic phenotype and affects outcome. Robust genetic variability occurs in genes controlling human angiogenesis, which may affect outcomes with anti-angiogenic therapies. In E2100, patients with VEGF -2578AA and -1154AA genotypes had prolonged overall survival but no difference in progression-free survival [10]. This may suggest an interaction between genotype and outcome after cessation of therapy, and that some subgroups experience unfavorable changes in the angiogenic milieu.

Another major issue is the proper duration of anti-angiogenic therapy. Unlike the 'patients' treated by Ebos and colleagues [5], adjuvant therapy patients receive far more than a week's work of sunitinib. Patients regularly receive adjuvant chemotherapy, adjuvant hormonal therapy (if estrogen receptor-positive) and trastuzumab (if HER2-positive). These therapies provide significant survival benefits, but more importantly synergize with anti-VEGF therapies in multiple preclinical models. Sunitinib monotherapy is the last thing one would attempt in the adjuvant setting, and 7 days of anti-VEGF therapy contrasts with anti-VEGF adjuvant trials administering from months to a year of anti-VEGF therapy.

So how worried should we be? Clinical trialists are always worried, and with good cause: trials routinely go wrong for multiple and unpredictable reasons. Duration in particular may be a concern in the adjuvant setting. Some adjuvant therapies (chemotherapy and trastuzumab) require fairly short durations of therapy, but others (for example, hormonal therapy) require years to maximize benefit. We simply do not know how long we will need to administer adjuvant anti-VEGF therapy.

Competing interests

GS has served as a consultant to Genentech, the maker of bevacizumab, which is mentioned in the article. BPS has received research funding from Genentech. The authors have no other competing interests.

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