Bevacizumab in Breast Cancer: The Best Is Yet to Come?

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This article is a review of Bevacizumab in the Treatment of Metastatic Breast Cancer.

Based on preclinical data, antiangiogenic therapy for cancer is both logical and rational. Tumors secrete proangiogenic factors, and the design of agents that target these factors has great potential to add to and in some cases replace cytotoxic chemotherapy.[1,2] The addition of bevacizumab (Avastin)—an anti–vascular endothelial growth factor (VEGF) humanized monoclonal antibody—to chemotherapy has changed practice in many tumor types including colon, lung, and breast.[3-5] Unfortunately, however, this drug is not the long-awaited panacea for which we as oncologists have hoped.

Initial Clinical Findings
As described in the review by Dr. Traina, bevacizumab initially showed promising activity in a heavily pretreated phase I breast cancer patient population, which led to investigations of the drug in combination with chemotherapy.[6] One of the earliest large combination studies with capecitabine (Xeloda) in metastatic breast cancer patients treated with at least one prior regimen demonstrated a near doubling of the response rate.[7] This did not, however, translate into an advantage in either progression-free or overall survival. A possible explanation for this result was that with the amount of prior treatment given to participants in this trial, the vasculature of the tumors was more established, and therefore strategies aimed at VEGF and blockade of these proangiogenic signals were less likely to be effective. Another potential explanation was that this randomized phase III study overestimated the time to progression in the control arm, and thus, was underpowered to detect progression-free or overall survival.

This prompted the evaluation of bevacizumab in metastatic breast cancer (MBC) patients who had not received prior chemotherapy for MBC, in Eastern Cooperative Oncology Group (ECOG) 2100.[5] Approximately 65% of the patients had received adjuvant chemotherapy, and 14% to 17% had prior taxane therapy. The chemotherapy of choice for this trial was paclitaxel given weekly, a schedule that is antiangiogenic in its own right.[8,9] There was a great deal of excitement about this combination when results were first presented at the American Society of Clinical Oncology (ASCO) annual meeting in May 2005. A that time, a doubling in response rate was accompanied by a near doubling in the progression-free survival.[10] The final analysis of this study, however, failed to show an improvement in overall survival.[5] This resulted in a large debate among US Food and Drug Administration (FDA) officials, oncologists, and patient advocates as to whether this drug truly provided meaningful improvements in patient outcome, or whether the FDA was lowering its standards for drug efficacy.

It is worth noting that many other drugs now considered standard of care in the treatment of breast cancer, such as aromatase inhibitors in the adjuvant setting, have not shown improvements in overall survival.[11] The difficulty in demonstrating an overall survival advantage in the first-line setting is a valid consideration, as the number and types of subsequent therapies play a large role in determining this outcome.

Current Status, Ongoing Trials
While the FDA’s Oncology Drugs Advisory Committee initially recommended against the approval of bevacizumab in the first-line setting, the FDA did grant accelerated approval of the drug, pending the results of ongoing studies. Due to the results seen in ECOG 2100 and the approval of the bevacizumab/paclitaxel combination for first-line treatment of MBC, this regimen has become a new benchmark in first-line treatment and is the “standard” arm in many current clinical trials, whether warranted or not.

The AVastin And DOcetaxel (AVADO) study similarly showed improvements in progression-free
survival and response rate when bevacizumab was given with every-3-week docetaxel (Taxotere). The magnitude of the effect, however, appeared to be much more modest in this study, with < 1 month absolute improvement in progress-free survival. Although statistically significant, these results are less impressive than those seen in ECOG 2100. It is unknown whether this is a reflection of less synergy between docetaxel and bevacizumab, a smaller antiangiogenic effect with docetaxel dosed every 3 weeks as compared to weekly paclitaxel, or other factors.

Regimens in Bevacizumab for Breast Oncology (RiBBOn-1) is an international randomized phase III trial comparing first-line chemotherapy for MBC (capecitabine, taxane, or anthracycline combinations) with or without bevacizumab. The results of this trial may be available at ASCO 2009. RiBBOn-2 compares second-line chemotherapy for MBC with or without bevacizumab. The results of the RiBBOn trials should help to solidify the role of bevacizumab in the first- and second-line settings in MBC therapy, as well as help to elucidate the optimal chemotherapy with which to combine it. A number of adjuvant studies with bevacizumab are ongoing. Preclinical modeling suggests that this may be the most efficacious setting for bevacizumab, as the blood supply of micrometastasis is much less established than that seen with visible metastatic disease and should theoretically be more sensitive to blockade. The setting of early-stage disease may provide the greatest niche for this particular antiangiogenic therapy in breast cancer. Additionally, other strategies to inhibit angiogenesis such as the use of small-molecule tyrosine kinase inhibitors have shown equally promising early data and are currently being explored in phase III comparisons to bevacizumab.[12]

Conclusions
Taken together, the evidence supports the use of bevacizumab in combination with chemotherapy in the first-line setting in MBC. Currently available data suggest that weekly paclitaxel is the chemotherapy of choice, although that may change with the results of the RiBBOn trials. Maintenance strategies involving the continuation of bevacizumab as a single agent after initial response to treatment have yet to be fully elucidated. Finally, it is important to note that toxicity must be appreciated with bevacizumab. While serious toxicity with this agent is rare, the potentially life-threatening complications of bevacizumab are not to be underestimated.


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