Targeting angiogenesis in cancer dates back to the 1970s, when the first anti-angiogenesis inhibitor, bevacizumab, was described to “starve tumors.” Of course in breast cancer, there was a lot of excitement when bevacizumab was granted accelerated approval by the Food and Drug Administration (FDA) in metastatic breast cancer in 2008 on the basis of three randomized trials in the first line HER2 negative metastatic breast cancer setting: E2100, AVADO, RIBBON-1 all met their primary endpoint of prolonging progression-free survival (PFS). Unfortunately, a subsequent meta-analysis confirmed a PFS of 2.5 months, which did not translate into an overall survival (OS) benefit. The lack of an OS benefit, in combination with increased toxicity, led to the FDA revoking the accelerated approval in 2011. Not only did this lead to a debate about why the PFS benefits did not translate into OS benefits, it also created questions about the appropriate endpoints for drug approval.

Yet the bevacizumab story did not end there—there were additional studies in the metastatic setting which did not lead to an improvement in outcomes. Studies in the neoadjuvant setting (NSABP B-40, GeparQuinto, CALGB 40603) did not lead to an improvement in pathologic complete response. However, there was a signal in subset analysis: Bevacizumab was favored in the hormone receptor positive subset in NSABP B-40 and in the triple negative breast cancer (TNBC) subset in GeparQuinto. In CALGB 40603, the addition of bevacizumab improved pathologic complete response in the TNBC subset but notably, pCR was defined as pCR in the breast only. Finally in the adjuvant setting, the BEATRICE and BETH studies in TNBC and HER2 positive breast cancer, respectively, did not show an improvement in disease free survival or OS with the addition of bevacizumab.

In the breast cancer oral session at ASCO, two additional studies of bevacizumab in breast cancer were presented. Kathy Miller presented E5103, a trial of bevacizumab in addition to chemotherapy in the adjuvant breast cancer setting. There was no improvement of invasive disease free survival (IDFS), but the arms containing bevacizumab had higher rates of hypertension, congestive heart failure, and discontinuation of adjuvant chemotherapy. Additionally, Olivier Tredan presented the AROBASE trial, in which patients received exemestane plus bevacizumab as maintenance therapy after first-line paclitaxel and bevacizumab. Patients with ER+/HER2- locally advanced or metastatic breast cancer who had not progressed after 16-24 weeks of 1st line paclitaxel plus bevacizumab therapy were randomized to continue the combination of paclitaxel plus bevacizumab versus endocrine therapy with exemestane plus bevacizumab. The primary endpoint was PFS. There was no statistically significant difference in PFS between the two arms.

The studies of bevacizumab in breast cancer raise several questions: Can predictive biomarkers identify those patients who will receive a benefit from treatment with bevacizumab? What is an appropriate endpoint for clinical trials? Is this the end of an era for bevacizumab in breast cancer? What about next generation anti-angiogenesis inhibitors? If we take a page from gastric cancer’s book, there very well might be. In the phase III AVAGAST trial in gastric cancer, bevacizumab for advanced gastric cancer did not improve overall survival. Yet ramucirumab, the next generation anti-angiogenesis inhibitor, was just approved by the FDA for use in advanced gastric cancer on the basis of the REGARD and RAINBOW Trials.
Peter Kaufman then presented a phase I trial of trebananib plus paclitaxel and trastuzumab in HER2-positive locally recurrent or metastatic breast cancer. Trebananib (AMG 386) is a recombinant peptide-Fc fusion protein that acts on the angiopoietin axis in angiogenesis. In TRINOVA-1, a phase-3 trial of patients with recurrent ovarian cancer, trebananib plus paclitaxel compared with placebo plus paclitaxel significantly improved PFS. The primary endpoint was to demonstrate the safety and tolerability of trebananib in combination with paclitaxel and trastuzumab in patients with HER2+ locally recurrent or metastatic breast cancer. The rationale for this combination is that HER2 signaling is associated with induction of angiogenesis. The combination proved to be tolerable. The most common adverse event was edema, which was predominantly grade 1 or 2 and generally manageable. Mechanism-specific toxicities also included hemorrhage and hypertension. There was no drug-drug interaction observed. Objective response rate (ORR), PFS, and duration of response (DOR) suggested that this regimen may have antitumor activity but additional trials are warranted. ORR was 88%. There were 2 DLTs: transient ischemic attack (TIA) and increased gamma glutamyltransferase. Treatment emergent AEs of interest were edema, hemorrhage, hypertension, pleural effusion, blurred vision, thromboembolic events and decreased LVEF. No AEs of GI perforation, ascites, impaired wound healing, or proteinuria were observed.

Perhaps trebananib represents a new era in antiangiogenesis therapies. In her discussion of the three trials, Erica Mayer stated that in the studies of bevacizumab, we have learned the importance and need of prospectively incorporating correlative biomarkers, and developing appropriate clinical trial endpoints, as well as the importance of post-approval monitoring for toxicity signals. She went on to say there does not appear to be a current or future role for bevacizumab in breast cancer, but perhaps there will be a role for other angiogenesis inhibitors in breast cancer.

Stay tuned...

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