Reevaluating Bevacizumab: The Role of VEGF Inhibitors in Metastatic Breast Cancer

by PAMELA HALLQUIST VIALE, RN, MS, CS, ANP, AOCNP®

Breast cancer remains a formidable disease. This tumor is the second most frequently occurring cancer in the world and the most commonly seen tumor type in women. Metastatic breast cancer (MBC) caused approximately 46,000 deaths in the United States for the year 2010 (Jemal, Siegel, Xu, & Ward, 2010). In general, women with MBC are considered incurable, although actual prognosis depends on the age of the patient, stage of disease, and hormone-receptor status (Hortobagyi, 2002). The goal of treatment for patients with MBC remains primarily to relieve symptoms, extend life, and improve quality of life, balancing risks of treatment with perceived benefit.

Bevacizumab (Avastin), a vascular endothelial growth factor (VEGF) inhibitor, was initially approved by the US Food and Drug Administration (FDA) for the treatment of metastatic HER2-negative breast cancer in 2008 (Pazdur, 2010). The agent was intended to be given in combination with paclitaxel for patients who met the criteria for the drug. This accelerated approval was granted despite the lack of data demonstrating an improvement in disease-related symptoms or increased overall survival (OS). The E2100 study was an open-label phase III trial with 722 patients randomized to receive paclitaxel plus bevacizumab or paclitaxel alone; the results demonstrated that patients receiving the combination experienced a significantly prolonged progression-free survival: 11.8 vs. 5.9 months (Miller et al., 2007). The objective response rate also showed an increase for the group receiving bevacizumab with paclitaxel vs. the group receiving paclitaxel alone (36.9% vs. 21.2%). However, the OS rate for the two groups was similar (26.7 vs. 25.2 months; hazard ratio, 0.88; $p = .16$). Of note, a 20% increase in grade 3

to 5 adverse events was seen in the patients receiving the combination vs. paclitaxel alone (Pazdur, 2010). Based on this single trial, the FDA granted accelerated approval for the drug's new indication.

Accelerated approval by the FDA is intended to provide patients with serious or life-threatening illnesses access to new medications; applications for new drugs or indications are reviewed by the Oncology Drugs Advisory Committee and then presented to the FDA (Viale & Moore, 2008). A key component of approval is that once the new drug or drug indication is approved by the FDA, postmarketing studies are mandated to observe for drug toxicities and determine ongoing clinical benefit (Viale & Moore, 2008). On December 16, 2010, the FDA announced their recommendation for removal of the breast cancer indication from the label of bevacizumab because the drug had not been shown to be safe and effective for that disease.

The recommendation was based on the review of results from four clinical studies of bevacizumab in women with breast cancer showing the lack of benefit in prolongation of overall survival or a sufficient benefit in the slowing of disease progression and the balance of risk vs. benefit. The risks identified were adverse events noted in patients receiving bevacizumab, including perforations, myocardial infarction, or heart failure. An independent advisory committee reviewed all available data and voted 12-1 to remove the breast cancer indication from the drug label. The process to finalize this action is a multistep one; the drug is still available and listed on the NCCN Guidelines as a treatment option in patents with metastatic disease (preferably with paclitaxel; NCCN, 2011). Appropriate medical judgment should be employed to determine whether treatment is warranted.

Advanced practitioners (APs) caring for this population should be prepared to answer patient queries regarding the possible withdrawal of bevacizumab in the treatment of women with MBC. Discussion of the risks and benefits of therapy along with a review of the most recent studies of bevacizumab and metastatic breast cancer is important. Postmarketing surveillance is an important part of our understanding of the true toxicities of new therapies and the determination of actual drug benefit. Advanced practitioners can play a key role in the reporting of unexpected toxicities of new therapies and in the communication of new study findings to our patients.

Inside This Issue

In this issue of the *Journal of the Advanced Practitioner in Oncology,* Sandra Kurtin and Sarah Daniel discuss pancreatic cancer and the role of the AP in the management of this often fatal cancer. Kristen Kreamer and colleagues present the final installment in our biomarkers series—a primer on biomarkers used in non–small cell lung cancer. In *Grand Rounds,* Paula Anastasia discusses carboplatin hypersensitivity and presents a desensitization protocol illustrated through an interesting case study.

You'll definitely want to read the *Practice Matters* article on ionizing radiation from Marcia Patterson, which shows us why we should work toward reducing the number of CT scans that patients receive. In *Prescriber's Corner*, Chris Campen and Emad Elquza present information on the prostate cancer drug cabazitaxel (Jevtana). In our *TRIP* section, Kathleen Clifford, Jeannine Brant, and Elizabeth Ciemins discuss the *NEJM* article by Temel et al. that reported on the proven benefits of adding palliative care to standard treatment in a study of patients with metastatic non–small cell lung cancer.

In *Tools & Technology,* Wendy Vogel and I suggest guidelines, tips, and resources for those of you who have considered scholarly writing but don't know how to start. Finally, in *Meeting News* we cover 3 of the 6 presentations from the 2011 NCCN Nursing Program this past March.

We hope you are enjoying *JADPRO*, and as always, we welcome your suggestions on what you'd like to read about!

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