Is the Battle Over Bevacizumab Coverage Looming?

The FDA's approval of the cancer drug bevacizumab (Avastin; Roche/Genentech) in February 2004 validated a 30-year-old theory, championed by Judah Folkman, MD, of Harvard, that tumors can be stopped by choking off their blood supply. Enthusiasm for the drug was almost universal, as investors said at the time that it could one day command $2 billion a year in global sales.¹

Seven years and 4 label expansions later, bevacizumab is Roche Holding AG's biggest product, with sales of 6.46 billion Swiss francs in 2010,² or $6.22 billion, based on the average annual exchange rate. The drug is approved in the United States for colorectal cancer, lung cancer, glioblastoma, kidney cancer, and breast cancer and is being tested in more than 50 tumor types.¹

The FDA announced in December that it planned to withdraw the drug's approval in breast cancer, where it has been widely used in advanced cancers. Breast cancer strikes 207,000 women in the United States each year and kills about 40,000. The news was striking in part because WellPoint Inc., UnitedHealth Group Inc., and other top insurers said they will continue to pay $8100 a month for the drug's use in breast cancer cases.

When asked for the basis of a decision that would undoubtedly increase their breast cancer treatment costs by millions, the insurers pointed to a recommendation by NCCN. How can it be that a little-known, nongovernmental advisory group carries greater credibility with health insurers than the FDA?

Avastin won conditional approval in the United States for treatment of metastatic HER2-negative tumors in 2008, based on preliminary evidence from a single study in which the drug slowed disease progression. The decision was a surprise because an FDA advisory panel recommended against expansion in a 5 to 4 vote, saying the benefits in breast cancer patients did not justify the risk of serious side effects.

Drugmakers are required to conduct follow-up studies to prove a medicine's suspected benefit as part of the FDA's accelerated approval program. When Roche's 2 follow-up studies failed to live up to the expectations created by the initial study, the agency called another advisory panel to review whether approval should be revoked. The new panel voted 12 to 1 that bevacizumab should no longer be marketed for breast cancer. The FDA began the process of finalizing that recommendation on December 16, 2010, the same day the European Medicines Agency said bevacizumab should still be used with paclitaxel in treating breast cancer.

Janet Woodcock, MD, head of the FDA's Center for Drug Evaluation and Research, says the “bottom line” for the agency is that bevacizumab has more serious side effects than chemotherapy alone and that progression-free survival in breast cancer is “only reasonably likely to be correlated with benefit.”³

Many doctors say bevacizumab helps keep breast cancer under control in some women, but that knowing who will benefit is difficult. As a result, the drug is used in many newly diagnosed patients.

“We can be sure that the benefit doesn’t extend to all patients, but it extends to a subset,” according to Eric Winer, MD, director of the breast oncology center at the Dana-Farber Cancer Institute. “Ultimately, we want to develop drugs that improve survival. But there are settings where we should accept less than that if we think that a drug can help women in other ways.”

Although doctors can continue to prescribe bevacizumab “off-label” if breast cancer is removed from the drug's approved indications, patient groups have worried that insurers may stop paying for it. Tim Anderson, MD, an analyst at Sanford

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Bernstein & Co., said in July that revoking FDA approval in breast cancer would cost Roche as much as $1 billion in future annual sales.

Several insurers, however, including UnitedHealth, WellPoint, Aetna Inc., and Humana Inc., say they will keep covering Avastin based on the NCCN's recommendation. Why aren’t these companies—the 4 largest insurers in the United States by revenue—listening to the FDA?

Alan Rosenberg, MD, vice president of medical policy for Indianapolis-based WellPoint, said his company believes the NCCN Guidelines are “strongly supported” by medicine. “We consider carefully what the FDA looks at, but we try to figure out what’s reasonable from a benefit perspective for our members,” Dr. Rosenberg said.

In 2008, Minnetonka, Minnesota–based UnitedHealth became the first insurer to base coverage on the NCCN Guidelines. These guidelines are now recognized in more than 100 countries as the standard in how to diagnose, treat, and reduce the risk of cancer.

The chair of the NCCN Guidelines Panel for Breast Cancer, Robert Carlson, MD, a medical oncologist at Stanford Comprehensive Cancer Center, said that continuing to recommend bevacizumab in metastatic breast cancer shows “logical consistency” because many approved drugs have also failed to show benefits in survival or quality of life. The panel discussed bevacizumab 3 times in the 4 to 5 months leading up to the FDA announcement, Dr. Carlson noted, “and was very cognizant that the FDA may withdraw approval.” After repeated review, the 27 members determined that there was “no new information in the current data sets that would alter the panel’s recommendation.”

The NCCN Guidelines Panel for Breast Cancer includes oncologists, pathologists, and a patient representative. One-third of the members have helped in clinical trials or consulted for Genentech, which developed bevacizumab, according to disclosures on the NCCN Web site. Panel members cannot stay on the panel if they receive more than $50,000 from outside companies or more than $20,000 from any one company, and the panel may choose to exclude members from certain discussions if there is a potential conflict of interest.

William McGivney, PhD, NCCN’s chief executive officer, says the widespread use of the NCCN Guidelines “speaks to the recognition and acceptance of the transparency, credibility, and authority” they have. “No other organization in medicine has attained this level of trust,” he said.

The FDA views NCCN as a “well-respected group of oncologists” whose recommendations sometimes differ from the agency’s decisions on approval, says Erica Jefferson, an FDA spokeswoman. Doctors should use their judgment when deciding what treatments to use “when FDA-approved treatments have been exhausted,” she said.

Roche filed an appeal with the FDA on January 18, 2011, proposing that a decision to withdraw approval in breast cancer be postponed until a new study examines the validity of a genetic biomarker that may show which patients will respond best to treatment. The company expects a response within 30 to 60 days on its request for a hearing with the FDA.

As this plays out, the reaction among insurers may be a case study in how they will resolve conflicting opinions in an era of targeted therapies that do not work for everyone.

“Health insurers have been vilified for years now because of their policies” in covering drugs, said Len Lichtenfeld, MD, deputy chief medical officer at the American Cancer Society. “It may be a matter of them choosing their battles.”
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References


