

Bevacizumab–associated diverticulitis

June M. McKoy, MD, MPH, JD,^{1,2} Jyoti Patel, MD,^{1,3} D. Mark Courtney, MD,⁴
Carlos R. Bolden, BS,⁵ and Charles L. Bennett, MD, PhD, MPP^{1,3,6}

¹ The Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; ² Division of Geriatric Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; ³ Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL; ⁴ Department of Emergency Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; ⁵ Feinberg School of Medicine, Northwestern University, Chicago, IL; ⁶ VA Midwest Center for Health Services and Policy Research, Jesse Brown VA Medical Center, Chicago, IL

This feature is designed to help protect your patients with updates on adverse events related to various cancer treatments.

Recently, instances of severe bevacizumab–associated diverticulitis have been reported. Investigators affiliated with the Research on Adverse Drug Events and Reports (RADAR), an established pharmacovigilance program, evaluated the frequency and clinical characteristics of bevacizumab (Avastin)–associated diverticulitis from clinical trial reports and spontaneous reports to the MedWatch program of the US Food and Drug Administration (FDA). Clinical features of bevacizumab–associated diverticulitis included abdominal pain, nausea, vomiting, fever, and peritonitis, requiring surgical intervention. Toxicity occurs after a median duration of 25 days after initiation of bevacizumab.

Where reported

A comprehensive review of the MedWatch database identified reports of 11 cases of bevacizumab–associated diverticulitis. No cases of diverticulitis were found with the antifolate pemetrexed (Alimta) alone. One case was found with pemetrexed and bevacizumab, and one case with pemetrexed, carboplatin, and bevacizumab. Our analysis sought to determine whether these cases had proportional reporting ratios (PRRs) that would suggest a relationship with bevacizumab or

carboplatin, finding no evidence of signals for these drugs.

In an abstract presented as a poster at the 2006 Annual Meeting of the American Society of Clinical Oncology, Jyoti Patel et al reported several findings from a clinical trial of pemetrexed and carboplatin plus bevacizumab for advanced non-squamous non-small cell lung cancer (NSCLC) between August 2005 and September 2006.¹ The most common grade 3/4 non-hematological toxicities included proteinuria (3%, n = 1, gr 3), venous thrombosis (3%, n = 1, gr 3), infection (3%, n = 1, gr 4), and diverticulitis (11%: 8%, n = 3, gr 3/3%, n = 1, gr 4). One patient with diverticulitis experienced bowel perforation requiring surgical intervention. The trial was temporarily suspended, and those patients with diverticulitis were analyzed separately. The only risk factor identified by the authors was a history of diverticulitis. No patient was neutropenic at the time nor did any patients have evidence of metastatic disease to bowel.

Additionally, Heinzerling et al found that patients with metastatic colon cancer receiving bevacizumab are at increased risk for diverticulitis and increased risk of bowel perforation.² The pathophysiology for the development of diverticulitis in patients with metastatic colon cancer is likely due to direct tumor involve-

ment. Explanations for the attendant bowel perforation include rapid lysis of a transmural tumor in response to therapy and ischemic events.

Recommendations

Bevacizumab appears to be linked to diverticulitis in settings where the

Fast Facts

BEVACIZUMAB

Bevacizumab (Avastin) is a monoclonal antibody that exerts its effect by attaching to and inhibiting the action of vascular endothelial growth factor, preventing the formation and growth of new blood vessels. It was the first such therapy, designed to inhibit angiogenesis, that was approved by the US Food and Drug Administration (FDA).

In 2004, the FDA approved the use of bevacizumab in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum. In 2006, the FDA approved bevacizumab for use in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC).

patient presents with underlying diverticular disease. Long-term clinical trials are needed to further evaluate this signal. In the interim, physicians should use bevacizumab with caution in this setting, especially in elderly patients already at risk for diverticular disease. We recommend that physicians maintain a high index of suspicion for this toxicity and report

the relevant clinical findings to the FDA's MedWatch program or to the RADAR program.

References

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2. Heinzerling JH, Huerta S. Bowel perforation from bevacizumab for the treatment of metastatic colon cancer: incidence, etiology, and management. *Curr Surg* 2006;63:334-337.

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Dr. Bennett is Associate Director at VA Midwest Center for Health Services and Policy Research, Chicago, IL. He is also affiliated with Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and VA Midwest Center for the Management of Complex Chronic Care, Jesse Brown VA Medical Center, Chicago, IL. He can be reached at cbenne@northwestern.edu.