Bevacizumab has shown efficacy in many different malignancies and is approved by the US Food and Drug Administration for advanced colon and lung cancers. As bevacizumab use is expanding, the number of reports of serious adverse effects from the drug are growing. Bowel perforation is a rare but often fatal event that leads the list of dangerous adverse effects. It has been frequently reported in ovarian cancer trials, with early closure of some trials because of the high incidence of bowel perforation. Physicians should be familiar with not only the presentation of bowel perforation, but also with the risk factors, considerations for surgery, and management of perforation in selected patient populations. The authors review the current knowledge on bevacizumab-induced bowel perforation.

**Mechanism of Perforation**

Several mechanisms of action have been described to explain the development of bowel perforation as a result of bevacizumab. In the first mechanism, the inhibition of VEGF by bevacizumab could cause thrombosis of smaller splanchnic or mesenteric vessels, leading to bowel ischemia and ultimately bowel perforation.\(^5\,6\) Vascular endothelial growth factor is involved in cytoprotection, proliferation of endothelial cells, and increased synthesis of nitric oxide and prostacyclin, as well as tissue plasminogen activator and urokinase. It also induces factor III, von Willebrand factor, and plasminogen activator inhibitor, which are all important in clotting and thrombosis.\(^7\) Bevacizumab inhibits these factors when it inhibits VEGF, which may lead to thrombosis or bleeding, depending on the delicate balance of these factors in an individual. Increased clot formation and vasoconstriction of the splanchnic vasculature could lead to bowel ischemia, which could in turn cause bowel perforation.\(^5\)

The second possible mechanism is related to bowel mucosa. Constant bowel wall proliferation and healing is dependent on microcirculation, protection with nitrous oxide, prostacyclin, and normal platelet function, all of which depend on VEGF. Intestinal healing after damage such as surgery is also dependent on all of these processes. Even without prior damage, the intestinal mucosa could be susceptible to ulcers and even perforation as a result of VEGF inhibition by bevacizumab, especially with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).\(^7\) Decreased prostacyclin levels can lead to decreased gastric protective secretions, which can cause increased damage to the intestinal wall and ulcers.\(^7\)

The third possible mechanism involves the mucosal invasion of tumor. Tumor structure may provide some stability to the intestinal wall itself, and tumor death creates an area of disruption susceptible to perforation.\(^5\,6\,8\)

Finally, the fourth possible mechanism, which has been observed in animal models, is the regression of normal blood vessels.\(^9\) When tissue is deprived of adequate blood supply,
there is an increased possibility of cell damage, necrosis, and perforation.

Risk Factors

Several risk factors for bowel perforation have been identified in clinical trials and case reports (Figure 1). Some of the most frequently reported established risks for perforation include history of bowel surgery, ulcers, and certain types of cancer.

Evidence has shown that peptic ulcers may be a clinically significant risk factor for perforation. Bevacizumab is associated with ulcers through its inhibition of VEGF. In a Dutch Colorectal Cancer Group phase III study with 755 patients (oxaliplatin, capcitabine, and bevacizumab vs the same regimen with the addition of cetuximab), Tol et al reported 12 patients who had bowel perforation and 4 patients who had gastric ulcers and bowel perforation. The authors recommended using endoscopic evaluation to screen patients receiving bevacizumab for potential ulcers, as they may have a significantly increased risk factor for perforation. Bevacizumab is anti-inflammatory drug.

Several cases of reported perforation occurred years after surgery and at the site of anastomosis, which may be because of incompletely healed bowel. Other potential risk factors for bowel perforation, like the increased number of pretreatments (ie, chemotherapy), have not shown a clear relationship. A high rate of perforation occurred when bevacizumab was used after surgery in patients with pancreatic cancer.

Certain types of cancer may also be risk factors for bowel perforation. Results of trials have reported bowel perforation rates as high as 8% in patients being treated for pancreatic tumor and as high as 15.4% in patients being treated for ovarian primary tumors, compared with rates of less than 2.5% in other trials. The ORBIT trial, which sought to evaluate bevacizumab for ovarian cancer, was closed early after 5 of 44 treated patients developed bowel perforations. All of the patients had platinum-resistant disease and bowel metastasis. In addition, it has been postulated that erlotinib, a drug for the treatment of locally advanced or metastatic non–small cell lung cancer, may interact with bevacizumab to cause perforation. However, only 1 case of bowel perforation associated with both drugs has been reported in the medical literature. In that case report, non–small cell lung cancer had metastasized to the bowel, which could have contributed to the weakening of the bowel wall. The stage of disease and number of prior chemotherapy treatments may be a factor in perforation risk.

Surgery may also increase the risk of bowel perforation. Several cases of reported perforation occurred years after surgery and at the site of anastomosis, which may be because of incompletely healed bowel. Other potential risk factors for bowel perforation, like the increased number of pretreatments (ie, chemotherapy), have not shown a clear relationship. A high rate of perforation occurred when bevacizumab was used after surgery in patients with pancreatic cancer.

With careful patient screening and selection, future trials may report lower rates of bevacizumab-associated bowel perforation.

Presentation and Diagnosis

Badgwell et al reported the largest retrospective case series (N=24) to date on bevacizumab-associated bowel perforation (Figure 2). Most patients (n=20) presented with abdominal pain, 1 had sepsis, and 3 were asymptomatic but had perforations detected during surveillance imaging. Six patients had initial plain abdominal radiographs, the results of which showed intraperitoneal air and fistulas. Twenty-two bowel perforations were diagnosed by means of computed tomography (CT) scan, 1 was diagnosed by means of fistulogram, and 1 was diagnosed postmortem by means of autopsy (the patient died quickly after initial presentation). Imaging results showed 19 patients had intraperitoneal air and 5 had a gastrointestinal or enterocutaneous fistula only.

Symptoms of bowel perforation, if present, are highly dependent on the site of involvement. Although 50% of bowel perforations that occur in patients with intact primary

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**Figure 1.** Risk factors known or suspected to contribute to bevacizumab-induced bowel perforation. Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
tumor involving the bowel will occur at the tumor site,\textsuperscript{15} any part of the bowel can be involved. Pelvic pain may occur with rectosigmoid colon perforation, while nausea, vomiting, and obstipation may occur with bowel obstruction.\textsuperscript{23} Gastrointestinal complaints should be given careful consideration, as bowel perforations may be hard to diagnose.

In the Dutch Colorectal Cancer Group phase III study,\textsuperscript{15} most cases (89\%) of perforation occurred within 15 weeks after the start of bevacizumab treatment and anywhere prior to the fifth cycle of chemotherapy. This period is when a physician must have the highest level of suspicion for perforation and lowest threshold for ordering diagnostic imaging. A radiograph of the kidneys, ureters, and bladder may show free peritoneal air, but CT should be considered the diagnostic study of choice because it may reveal pneumoperitoneum, small bowel loops caused by obstruction, or even pneumatosis intestinalis.\textsuperscript{24,25}

\section*{Treatment}

The best approach to bowel perforation in patients receiving bevacizumab is surveillance and prevention. For example, when steroids and NSAIDs are used together, use of either a proton pump inhibitor or a prostaglandin agonist should be considered to prevent peptic ulcer disease, which is an exacerbating factor to perforation.

Another approach to prevention involves careful consideration when giving bevacizumab to patients who are undergoing or have undergone elective surgery. Current recommendations for elective surgery include a 60-day wait period after bevacizumab administration and a 30- to 60-day wait period to restart bevacizumab therapy after surgery.\textsuperscript{24} However, several cases of reported perforation have occurred years after surgery.\textsuperscript{10,26} Thus, even a 60-day wait period may not be enough for some patients with slower healing. Ongoing inflammation and granulation may occur for years after surgery and may carry a substantial risk for perforation.\textsuperscript{26}

Although the average reported bevacizumab half-life is 20 days, it can range from 11 days to 50 days,\textsuperscript{2} making a 60-day wait period for elective surgery risky for some patients.\textsuperscript{9} Another consideration is that clearance of bevacizumab has been reported to be 20\% lower in women than in men.\textsuperscript{2} If at all possible, the wait period for elective surgery should be at least 3 half-lives of the drug (or until 87.5\% of the drug is eliminated). In most patients, this period would be about 60 hours (with a 20-hour half-life), but in some patients it could be up to 150 days.\textsuperscript{2}

Abdominal CT scans can be used to assess bowel healing at a past resection or anastomosis site and to evaluate the presence of other potential risk factors such as rectovaginal nodularity, bowel wall thickening, diverticulitis, bowel obstruction, and colitis.\textsuperscript{26} If the benefit of bevacizumab therapy is relatively low in a patient with multiple risk factors or if inflammation of the bowel wall can be seen on results from a CT scan, then the risks of surgery may outweigh the benefits. Radiologists should be asked to focus on the anastomosis site and report any inflammatory changes present, otherwise smaller important findings may be read as unremarkable. Future trials should assess this approach in high-risk patients such as those with ovarian and pancreatic cancer, and exclude or delay enrollment of patients into bevacizumab protocols with incompletely healed surgical sites.

Once bowel perforation does occur in patients receiving bevacizumab, the perforation is managed conservatively or surgically. The decision regarding treatment can be complicated because patients typically have a terminal illness and are taking a drug that causes poor wound healing and dysfunc-

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig2.png}
\caption{Presenting signs and symptoms of bowel perforation in 24 patients treated with bevacizumab.\textsuperscript{12} *Specific signs included mental status changes, fever, tachycardia (>120 beats per minute), and leukocytosis.}
\end{figure}
tional platelets. The mortality rate for patients with bevacizumab-induced bowel perforation has been reported as high as 50%. For this reason, patients with multiple risk factors (e.g., recent surgery, radiologic evidence of incompletely healed bowel, a pretreated tumor with multiple chemotherapy regimens) may be considered for alternative regimens if the goal is palliation.

In the study by Badgwell et al. with 24 patients, 4 patients were treated surgically and 20 were treated conservatively. No patients died after surgery. In the conservative group, 3 patients died within 30 days after bowel perforation and 6 died within 60 days after perforation. However, it should be noted that the 3 patients who died during the first 3 months after bowel perforation were deemed nonoperative due to advanced carcinomatosis. Therefore, their deaths could not be directly attributed to perforation. Although all of the cases in the Badgwell et al. study would have been considered surgical, most were successfully managed with conservative treatment.

Whether conservative management or surgery is the best approach remains to be determined in future clinical trials. In the meantime, the decision regarding surgery should be based on individual severity of perforation, clinical signs, expectations of outcome, the patient’s wishes, and risks of bleeding and morbidity. If a patient is treated with surgery, bevacizumab therapy should not be restarted after recovery because of increased risk of recurrent perforation.27

Looking Forward

Although the results of some studies have shown increased risk of bowel perforation in patients with ovarian and pancreatic tumors, these data should not prevent future bevacizumab trials in such patients. With proper screening and use of exclusion criteria, the risk of perforation in patients with ovarian and pancreatic tumors could be reduced to the level of risk found in other cancer trials. Selecting patients with tumors in early stages who have had few prior treatments seems to underlie the success of some ovarian trials showing comparable perforation rates to other tumor treatments with bevacizumab. In addition, bevacizumab in combination with other chemotherapy as a first line therapy has shown similar curative promise with potentially fewer cases of hypertension and perforation. Future studies, like Gynecology Oncology Group 216, which is testing the use of carboplatin and paclitaxel with or without bevacizumab, will help clarify bevacizumab as a first line combination therapy.

Conclusion

Bowel perforation is a potential—and potentially fatal—adverse effect of bevacizumab therapy. Previous imaging studies may also be examined to identify risk factors, which could help exclude patients from bevacizumab protocols if they are at increased risk for bowel perforation. These steps should be taken in future clinical trials.

References


