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ORIGINAL REPORT

Risk Factors for GI Adverse Events in a Phase III Randomized Trial of Bevacizumab in First-Line Therapy of Advanced Ovarian Cancer: A Gynecologic Oncology Group Study

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To evaluate risk factors for GI adverse events (AEs) within a phase III trial of bevacizumab in first-line ovarian cancer therapy.

Patients and Methods
Women with previously untreated advanced disease after surgery were randomly allocated to six cycles of platinum-taxane chemotherapy plus placebo cycles (C)2 to C22 (R1); chemotherapy plus bevacizumab C2 to C6 plus placebo C7 to C22 (R2); or chemotherapy plus bevacizumab C2 to C22 (R3). Patients were evaluated for history or on-study development of potential risk factors for GI AEs defined as grade ≥ 2 perforation, fistula, necrosis, or hemorrhage.

Results
Of 1,873 patients enrolled, 1,759 (94%) were evaluable, and 2.8% (50 of 1,759) experienced a GI AE: 10 of 587 (1.7%, R1), 20 of 587 (3.4%, R2), and 20 of 585 (3.4%, R3). Univariable analyses indicated that previous treatment of inflammatory bowel disease (IBD; $P = .005$) and small bowel resection (SBR; $P = .032$) or large bowel resection (LBR; $P = .012$) at primary surgery were significantly associated with a GI AE. The multivariable estimated relative odds of a GI AE were 13.4 (95% CI, 3.44 to 52.3; $P < .001$) for IBD; 2.05 (95% CI, 1.09 to 3.88; $P = .026$) for LBR; 1.95 (95% CI, 0.894 to 4.25; $P = .093$) for SBR; and 2.15 for bevacizumab exposure (aggregated 95% CI, 1.05 to 4.40; $P = .036$).

Conclusion
History of treatment for IBD, and bowel resection at primary surgery, increase the odds of GI AEs in patients receiving first-line platinum-taxane chemotherapy for advanced ovarian cancer. After accounting for these risk factors, concurrent bevacizumab doubles the odds of a GI AE, but is not appreciably increased by continuation beyond chemotherapy.

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INTRODUCTION

Angiogenesis is a process integral to disease progression for solid tumors including ovarian cancer and is largely promoted by vascular endothelial growth factor (VEGF).[1-17] Bevacizumab, a VEGF neutralizing monoclonal antibody,[18] has demonstrated single agent activity in phase II ovarian cancer trials.[19,20] Results of four phase III trials have been reported, all demonstrating significant prolongation of progression-free survival when bevacizumab was combined with and continued beyond standard chemotherapy.[21-24]

The incorporation of bevacizumab into first-line ovarian cancer therapy has been controversial because of lack of an overall survival benefit as yet demonstrated for the entire study populations in the two first-line phase III trials[22,23] and to concerns related to additional toxicity.[25] GI wall disruption is perhaps the most concerning adverse effect associated with bevacizumab and has been reported in approximately 2.4% in general.[25] In the phase III first-line ovarian cancer trials, the aggregate rate was 2.9% for 1,960 women allocated to receive bevacizumab and 1.7% for 1,354 in the control groups. The pathogenesis for this complication in the setting

of bevacizumab therapy remains unclear, and specific risk factors have been suggested only through historical studies. Therefore, the Gynecologic Oncology Group (GOG) conducted a preplanned study embedded within its first-line phase III trial.

PATIENTS AND METHODS

As shown in Figure 1, GOG 0218[22] was a double-blind, placebo controlled first-line phase III clinical trial in which women with advanced cancers were randomly allocated to one of three postoperative regimens: six cycles of intravenous carboplatin-paclitaxel chemotherapy cycles (C) 2 to C22 (R1); chemotherapy plus bevacizumab (15 mg/kg) C2 to C6 (R2); and chemotherapy plus bevacizumab C2 to C22 (R3). Participation required stage III incompletely resectable intra-abdominal disease or stage IV disease and a GOG performance status (PS) of 0 to 2. Because of concerns regarding the risk of GI perforation, patients with evidence of intestinal obstruction requiring parenteral hydration or nutrition were excluded. Safety was monitored through physical and laboratory assessment after each treatment cycle by using National Cancer Institute Common Toxicity Criteria version 3.

The presence or absence of potential baseline risk factors for the development of GI adverse events (AEs) including surgical, vascular, hematologic, and inflammatory conditions was collected on a medical history (MEDH) form (online only). Other putative risk factors derived from the database at the completion of the trial included age at enrollment; GOGPS; the combination of stage and debulking level; time from surgery to C1 treatment; time from surgery to C2 treatment; and on-study development of intestinal obstruction, complicated (febrile or grade 4) neutropenia, or thromboembolic events.

GI AEs were defined as grade ≥ 2 perforation, fistula, necrosis, or hemorrhage occurring as of C2 (when bevacizumab or placebo was initiated) and ≤ 30 days of last protocol treatment.

The primary analysis of the clinical trial was based on progression-free survival and was conducted after 423 disease progression events or deaths had been reported. The current study is based on data collected up to the time of the primary data freeze, including only those with collected MEDH forms. Univariable analyses to test the association of GI AEs with potential risk factors were performed by using Fisher's exact test for discrete variables and a logistic model for continuous variables.[26] A logistic model was used to estimate the relative odds of a GI AE event because of bevacizumab, adjusted for other risk factors.[27] A time-dependent proportional hazards model was used to evaluate the null hypothesis that the onset of febrile neutropenia, intestinal obstruction, or thromboembolic events was not associated with subsequent onset of a GI AE.[28] All *P* values are two-sided.

RESULTS

Patient Characteristics

Baseline characteristics of the 1,873 patients enrolled onto GOG 0218 were similarly distributed across treatment groups (Table 1). The median age was 60 years, over 80% had serous adenocarcinomas, and the majority of cancers were grade 3. Forty percent had stage III disease with residual intra-abdominal tumor implants > 1 cm in diameter after primary cytoreductive surgery, and 26% had stage IV disease.

MEDH forms were collected on 1,759 (94%) of the 1,873 patients enrolled. As shown in Table 2, the frequency of putative medical risk factors for GI AEs was similarly distributed across the three treatment groups. Of note, at least 30% of patients had a vascular risk factor, with 582 (33%) under current medical management for hypertension and 226 (12.8%) having smoked within the previous year. With respect to GI conditions, 147 patients (8.3%) underwent small bowel resection

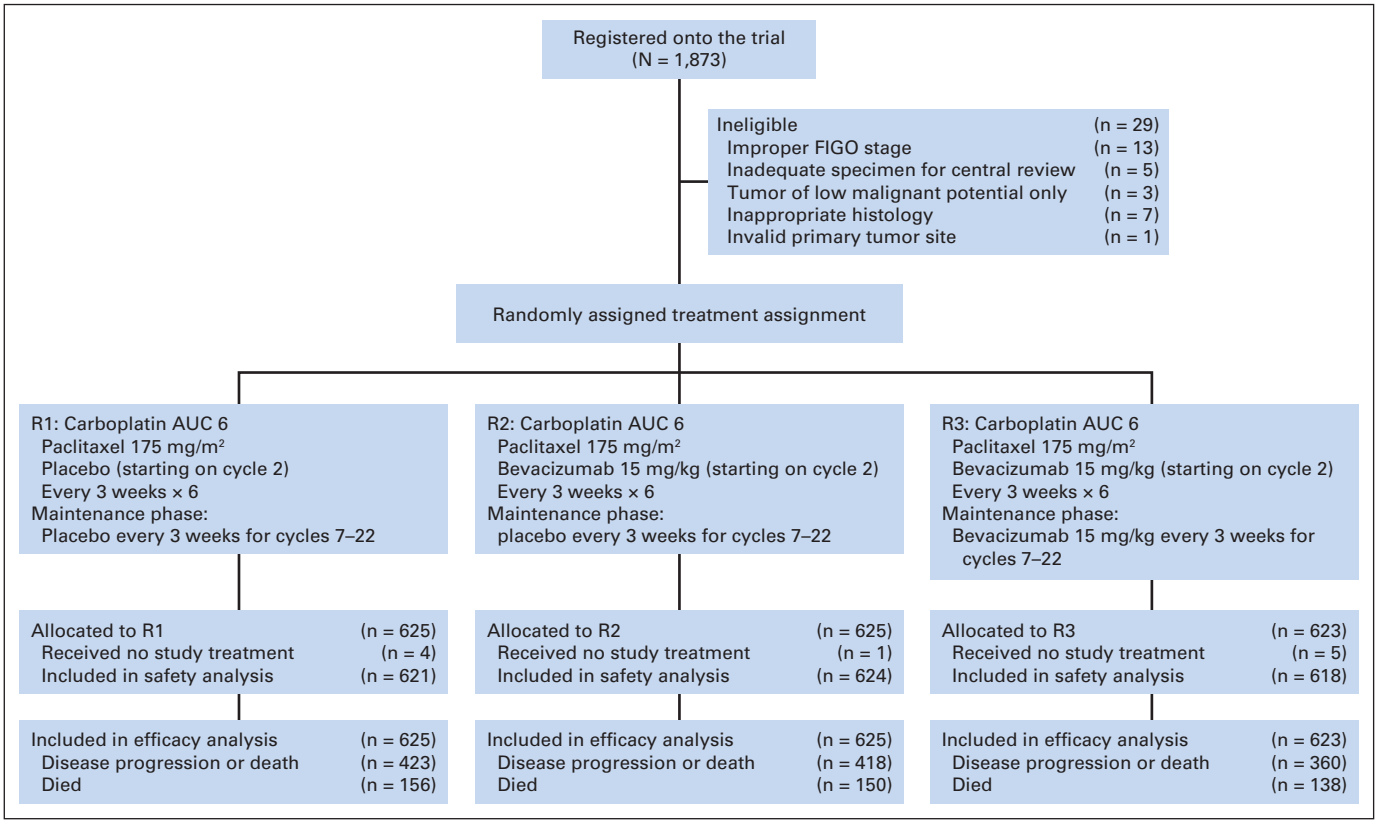

Fig 1. CONSORT diagram. AUC, area under the curve; FIGO, International Federation of Gynecology and Obstetrics staging system.

Table 1. Baseline Characteristics of the Source Population

Characteristic	R1 (n = 625) No.	%	R2 (n = 625) No.	%	R3 (n = 623) No.	%
Age						
Median	60		60		60	
Range	25-86		24-88		22-89	
Race*						
Non-Hispanic white	526	84	519	83	521	84
Asian	41	7	37	6	39	6
Non-Hispanic black	25	4	28	5	27	4
Hispanic	21	3	28	5	25	4
Other, specified	8	1	5	< 1	4	< 1
GOG PS						
0	311	50	315	50	305	49
1	272	44	270	43	267	43
2	42	7	40	6	51	8
Stage surgical tumor debulking level†						
III (macro) ≤ 1 cm‡	218	35	205	33	216	35
III > 1 cm§	254	41	256	41	242	39
IV	153	25	164	26	165	27
Histology‖						
Serous	541	87	519	83	524	84
Endometrioid	21	3	14	2	24	4
Clear cell	12	2	23	4	20	3
Mucinous	6	1	5	< 1	8	1
Other/not specified	45	7	64	10	47	7
Tumor grade‖						
3	445	71	465	74	460	74
2	102	16	86	14	97	16
1	36	6	28	4	18	3
Not specified	42	7	46	7	48	8

NOTE. All clear cell tumors classified grade 3.

Abbreviations: GOG, Gynecologic Oncology Group; PS, performance status; R1, chemotherapy plus placebo followed by placebo; R2, chemotherapy + bevacizumab followed by placebo; R3, chemotherapy + bevacizumab followed by bevacizumab.

*Percentages may not total 100% because of rounding or categorization.

†International Federation of Gynecology and Obstetrics.

‡Stage III with ≤ 1 cm maximal diameter for any residual abdominal tumor.

§Stage III with > 1 cm maximal diameter disease in any residual abdominal tumor.

‖Results from central GOG Pathology Committee review updated September 2010.

Table 2. Distribution of Medical History Risk Factors by Randomized Treatment Group

	R1 (n = 587) No.	%	R2 (n = 587) No.	%	R3 (n = 585) No.	%	Total (N = 1,759) No.	%
Currently takes medication for hypertension	191	32.5	201	34.2	190	32.5	582	33.0
Has in the past taken medication for hypertension	30	5.1	34	5.8	25	4.3	89	5.1
Ever had peripheral vascular disease with claudication	5	0.8	2	0.3	3	0.5	10	0.5
Ever had myocardial infarct or cerebrovascular accident	11	1.9	16	2.7	15	2.6	42	2.3
Smoked within past year	81	13.8	77	13.1	68	11.6	226	12.8
Currently takes insulin for diabetes	9	1.5	11	1.9	12	2.0	32	1.8
Currently takes oral medication for diabetes	31	5.3	42	7.2	42	7.2	115	6.5
Ever diagnosed with autoimmune disease	16	2.7	15	2.6	15	2.6	46	2.6
Ever had a peptic ulcer	11	1.9	15	2.6	11	1.9	37	2.1
Ever had an intestinal obstruction radiographically	16	2.7	18	3.1	18	3.1	52	3.0
Ever diagnosed with Crohn disease	2	0.3	1	0.2	1	0.2	4	0.2
Ever diagnosed with ulcerative colitis	6	1.0	7	1.2	3	0.5	16	0.9
Ever had medication or surgery for inflammatory bowel disease	7	1.2	3	0.5	3	0.5	13	0.7
Ever had medication, hospitalization, antibiotics, or dietary modification for diverticulitis	8	1.4	16	2.7	12	2.0	36	2.0
Ever had *Clostridium difficile* colitis	11	1.9	8	1.3	11	1.9	30	1.7
Ever had small bowel resection with anastomosis	53	9.3	51	8.7	54	9.2	158	9.0
Had small bowel resection at primary surgery	48	8.2	48	8.2	51	8.7	147	8.3
Ever had a large bowel resection with anastomosis	95	16.2	113	19.2	114	19.5	322	18.3
Had large bowel resection at primary surgery	90	15.3	108	18.4	108	18.5	306	17.4
Uses corticosteroids for a chronic condition	11	1.9	8	1.4	11	1.9	30	1.7
Uses NSAID chronically	38	6.5	34	5.8	38	6.5	110	6.3

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; R1, chemotherapy plus placebo followed by placebo; R2, chemotherapy + bevacizumab followed by placebo; R3, chemotherapy + bevacizumab followed by bevacizumab.

(SBR), and 306 (17.4%) underwent large bowel resection (LBR) at primary surgery for ovarian cancer. Relatively few had pre-existing Crohn disease or ulcerative colitis.

The rates of potential risk factors developing after enrollment but during treatment were low, including 39 patients (2.2%) with GI obstruction, 86 (4.9%) with complicated neutropenia (either febrile or grade 4), and 100 (5.7%) with either arterial or venous thromboembolic events.

Incidence and Spectrum of GI AEs

Fifty-seven patients (3.2%) experienced a GI AE overall, and in 50 patients (2.8%), the event occurred during or beyond treatment C2 (start of bevacizumab or placebo). Three patients (one patient with grade 3 hemorrhage, one with grade 3 fistula, and one with grade 5 bowel necrosis) are excluded from this report because for these cases a MEDH case report form was not submitted. As shown in Table 3, the most common type of GI AE was perforation in 20 patients (40%), followed by hemorrhage in 14 (28%) and fistula in 12 (24%). GI AEs were reported in 10 of 587 patients (1.7%), 20 of 587 (3.4%), and 20 of 585 (3.4%) for patients assigned to R1, R2, and R3, respectively. Although there were no grade 4 or 5 events in the R1 treatment group, events classified as life-threatening or fatal occurred in six (1%) in the R2 group and four (0.7%) in the R3 group. Figure 2 illustrates the

Table 3. Number of Grade 2 or Worse GI Adverse Event at or Beyond Cycle 2 by Type, Grade, and Treatment Group

GI Adverse Event Type	R1				R2				R3				Total
	2	3	4	5	2	3	4	5	2	3	4	5	
Fistula	1	3	0	0	1	2	1	0	1	3	0	0	12
GI leak	0	0	0	0	0	0	0	0	0	1	2	0	3
Necrosis	0	1	0	0	0	0	0	0	0	0	0	0	1
Perforation	0	2	0	0	1	5	2	3	0	5	0	2	20
Bleeding	2	1	0	0	3	2	0	0	3	3	0	0	14
Total	3	7	0	0	5	9	3	3	4	12	2	2	50*

Abbreviations: R1, chemotherapy plus placebo followed by placebo; R2, chemotherapy + bevacizumab followed by placebo; R3, chemotherapy + bevacizumab followed by bevacizumab.

*Three patients who experienced a grade 2 or worse GI adverse event after cycle 2 had no medical history form submitted and are therefore not included in this table or the rest of this report.

timing of events as a function of treatment group and cycle. Forty-six (92%) occurred during C2 through C6 (chemotherapy phase), with 38 (75%) reported by C4.

Association Between Risk Factors and GI AEs

Univariable analysis indicated no association of GI AEs with age at enrollment ($P = .593$), baseline PS ($P = .297$), the combination of stage and residual disease after debulking surgery ($P = .378$), time from surgery to C1 treatment ($P = .625$), or time from surgery to C2 treatment ($P = .997$; data not shown). There was also no significant association between a GI AE and on-study development of GI obstruction ($P = .625$), thromboembolic events ($P = .202$), or complicated neutropenia ($P = .094$, online only). In the time-dependent proportional hazards model, the odds of a GI AE was greater among the 74 patients in the study population who experienced febrile neutropenia before the onset of the GI AE, with a hazard ratio of 2.55 (95% confidence limits, 0.607 to 10.74), but this was not statistically significant ($P = .201$).

As shown in Table 4, a significant association with a GI AE was observed for history of inflammatory bowel disease (IBD; $P = .020$) or treatment of IBD ($P = .005$); SBR with anastomosis ($P = .039$) or SBR at primary surgery ($P = .032$); and LBR with anastomosis ($P = .016$) or LBR at primary surgery ($P = .012$). A multivariable logistic model was used to estimate the odds of a GI AE associated with bevacizumab, adjusted for significantly associated risk factors: IBD treatment, SBR at primary surgery, and LBR at primary surgery. Relative to R1, the odds of a GI AE were 2.15 (95% CI, 0.981 to 4.71) for R2 and 2.15 (95% CI, 0.981 to 4.70) for R3. Because the odds of a GI AE in each of the bevacizumab treated groups relative to placebo were similar, these two groups were combined into a single group to provide a more precise estimate of the effect of bevacizumab relative to placebo. As shown in Table 5, multivariable analysis estimated that bevacizumab independently increases the incidence of a GI AE by 2.15 (95% CI, 1.049 to 4.40; exact $P = .032$), which is similar to the univariable estimate, 2.19. Previous treatment of IBD and LBR at primary surgery were also independently associated with increased odds, whereas the impact on increased odds for SBR was similar in magnitude to LBR but was not statistically significant ($P = .093$).

Finally, a logistic model with a treatment-factor interaction term demonstrated no clear evidence that bevacizumab increased the odds ($P > .10$) of a GI AE associated with risk factors found to be significant in univariable analyses (data not shown).

DISCUSSION

To our knowledge, this is the first prospective study examining risk factors for serious GI AEs in the context of treatment of solid tumors with anti-VEGF agents.

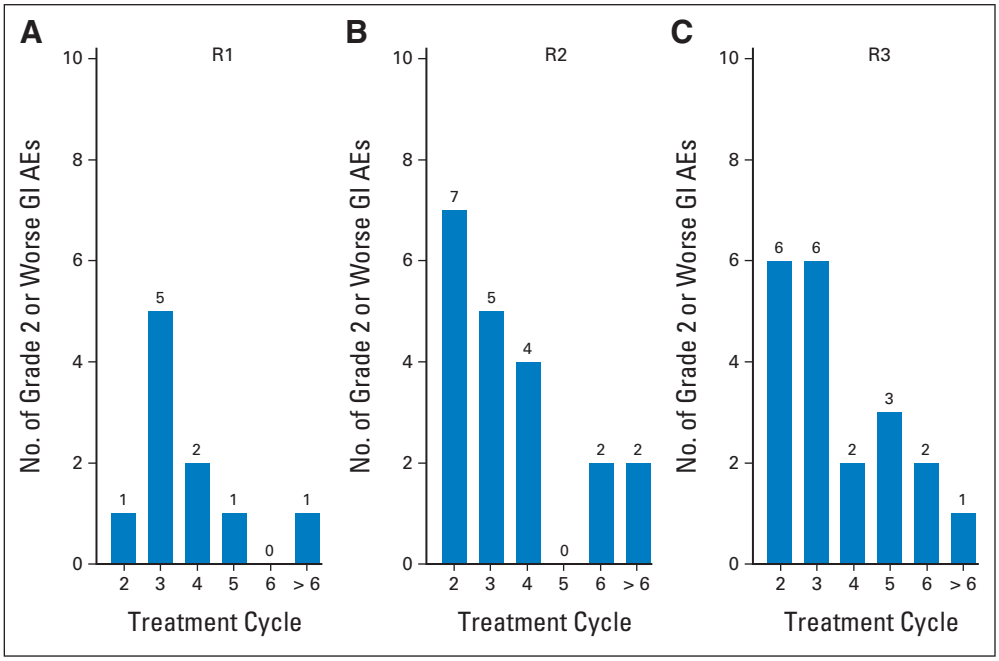

Fig 2. Number of treatment cycles before grade 2 or worse GI adverse event (AE). There were seven GI AEs before treatment cycle 2 that are not included in this figure. R1, chemotherapy plus placebo followed by placebo; R2, chemotherapy + bevacizumab followed by placebo; R3, chemotherapy + bevacizumab followed by bevacizumab.

Table 4. Univariable Analyses of Medical History Risk Factors and Development of a GI Adverse Event

	− GI AE (n = 1,709)		+ GI AE (n = 50)		
	No.	%	No.	%	*P*
Medication for hypertension					.170
Never	1,063	98	25	2.3	
Past	86	97	3	3.4	
Current	560	96	22	3.8	
Peripheral vascular disease with claudication					1.00
Never	1,699	97	50	2.9	
Ever	10	100	0.0	0.0	
Myocardial infarct or cerebrovascular accident					.114
Never	1,670	97	47	2.7	
Ever	39	93	3	7.1	
Smoked within past year					.829
No	1,490	97	43	2.8	
Yes	219	97	7	3.1	
Current medication for diabetes					.909
No	1,566	97	46	2.9	
Oral	112	97	3	2.6	
Insulin	31	97	1	3.1	
Diagnosis of autoimmune disease					.379
Never	1,665	97	48	2.8	
Ever	44	96	2	4.4	
Peptic ulcer					.624
Never	1,672	97	50	2.9	
Ever	37	100	0	0.0	
Intestinal obstruction radiographically					.658
Never	1,659	97	48	2.8	
Ever	50	96	2	3.9	
Diagnosis of IBD					.020
Never	1,692	97	47	2.7	
Crohn disease	4	100	0	0.0	
UC	13	81	3	18.75	
Medication or surgery for IBD					.005
Never	1,699	97	47	2.7	
Ever	10	77	3	23	
Medication, hospitalization, antibiotics, or dietary modification for diverticulitis					1.000
Never	1,674	97	49	2.8	
Ever	35	97	1	2.8	
Diagnosis of *Clostridium difficile* colitis					.209
Never	1,681	97	48	2.8	
Ever	28	93	2	6.7	
SBR with anastomosis					.039
Never	1,560	97	41	2.6	
Ever	149	94	9	5.7	
SBR at primary surgery					.032
No	1,571	97	41	2.5	
Yes	138	94	9	6.1	
LBR with anastomosis					.016
Never	1,403	97	34	2.4	
Ever	306	95	16	5.0	
LBR at primary surgery					.012
No	1,419	98	34	2.3	
Yes	290	95	16	5.2	
Current corticosteroids for a chronic condition					.582
Yes	1,680	97	49	2.8	
No	29	97	1	3.3	
Current chronic NSAID use					.367
Yes	1,600	97	49	3.0	
No	109	99	1	0.9	

Abbreviations: AE, adverse event; IBD, inflammatory bowel disease; LBR, large bowel resection; NSAID, nonsteroidal anti-inflammatory drug; SBR, small bowel resection; UC, ulcerative colitis.

In the initial report for GOG 0218, GI events were classified as grade ≥ 2 perforation, fistula, necrosis, or leak, and the rates of these events during or after treatment cycle 2 were 1.2%, 2.8%, and 2.6% for those enrolled to R1, R2, and R3, respectively.[22] Although one may consider these rates to be relatively low, they should be considered clinically meaningful, as events are often life threatening,[29,30] frequently require major surgical intervention, and may have long-term adverse consequences. Thus, it is important that independent and interactive risk factors for these complications are identified, allowing for refined risk assessment, creation of guidelines for patient counseling, development of preventive strategies, and generation of hypotheses related to underlying pathogenic mechanisms.

In the current study, GI AEs also included ≥ grade 2 GI hemorrhage, because mucosal ulceration manifested as bleeding was hypothesized to be mechanistically related to perforation on the basis of pathology studies.[31] Using our modified definition for the current study, the rate of GI AEs was 3.4% in each bevacizumab treatment group, approximately double that seen in the group assigned to chemotherapy alone and, not unexpectedly, remained an independent risk factor in multivariable analysis. We examined only events after initiation of bevacizumab or placebo to accurately factor in relative odds attributable to bevacizumab.

Table 5. Results of a Logistic Model Assessing the Association Between GI Adverse Events and Risk Factors Significantly Associated With GI Adverse Events in Univariable Analyses

	Relative Odds of Grade ≥ 2 GI AE		
Model Covariate	Estimated Odds	95% CI	*P*
IBD treatment	13.40	3.44 to 52.30	< .001
LBR at primary surgery	2.05	1.09 to 3.88	.026
SBR at primary surgery	1.95	0.894 to 4.25	.093
BEV treatment	2.15	1.05 to 4.40	.032

Abbreviations: AE, adverse event; BEV, bevacizumab; IBD, inflammatory bowel disease; LBR, large bowel resection; SBR, small bowel resection.

The finding that bevacizumab exposure was associated with increased odds of a GI AE with an odds ratio of 2.15 in the current study is supported by a meta-analysis by Hapani et al[29] examining 12,294 patients with a variety of nongynecologic solid tumors from 17 randomized controlled trials. This demonstrated the incidence of GI perforation to be 0.9% among patients receiving bevacizumab and the relative odds of GI perforation compared with control patients to be 2.14 (95% CI, 1.19 to 3.85; $P = 0.011$). Interestingly, in the current study, the odds ratio for the association of bevacizumab exposure with a GI AE was identical (2.15) for both those receiving bevacizumab only during the chemotherapy phase and those receiving bevacizumab during and continued beyond the chemotherapy phase, suggesting that there is no significant additional risk of bevacizumab continued beyond primary platinum-taxane chemotherapy.

The etiology of GI AEs as defined above has been found to be multifactorial and include traumatic, vascular, infectious/inflammatory, or toxic insults to the GI tract with impairment in healing as the common denominator.[29] This explains our selection of hypothetical risk factors for investigation. Except for bevacizumab exposure, all risk factors examined were similarly distributed across treatment groups in the clinical trial. We found that the odds of a GI AE was significantly associated with bevacizumab exposure; history of IBD or treatment of IBD; and previous SBR/LBR with anastomosis or SBR/LBR at time of primary surgery before enrolling onto GOG 0218.

Although the mechanisms by which bevacizumab may contribute to development of bowel perforation remain elusive, the preponderance of data suggests impairment of healing at sites of GI injury to be the common denominator. Early preclinical studies before the development of an anti-VEGF monoclonal antibody demonstrated several naturally occurring and synthetic antiangiogenic agents to impair healing after cutaneous surgical trauma[32,33] and colonic anastomoses,[34,35] whereas others demonstrated no clear impact on healing of cutaneous wounds despite reduction in micro-vascular maturation and granulation tissue.[36-39] Data pooled from two positive phase III randomized trials of bevacizumab in first-line therapy of metastatic colorectal cancer involving 1,132 patients demonstrated surgical wound healing complications in 1.3% of those receiving bevacizumab versus 0.5% in control patients. Though inconclusive, bevacizumab induced necrosis of tumor invading the bowel wall as an alternative process is suggested by retrospective analyses of clinical,[40,41] pathologic,[30,42] and radiologic[20] data. Indeed, the odds for GI perforation appear to be greater for patients with tumors involving the abdominal cavity, such as colorectal,[29] renal cell,[29] and ovarian,[43] which suggests that this is a possible mechanism. However, one cannot exclude the possibility that such tumors are more likely to be associated with confounding factors, such as tumor infiltration of the mesentery with compromise blood supply, intestinal obstruction, and previous intestinal surgery. In addition, this would not explain the association of such events with bevacizumab in patients with cancer who have no evidence of intra-abdominal tumor and no other obvious risks.[29,44] A limitation of the current study is our inability to examine GI wall involvement by tumor prospectively because no reliable methods of diagnosis or documentation have been established. Another possibility is that bevacizumab could limit the blood flow to the splanchnic microvasculature via thrombosis or vasoconstriction,[45,46] leading to GI ischemia, but evidence for this hypothesis is limited.

We also found that history of bowel resection was associated with a two- to threefold increase in the odds of a GI AE. The vast majority of GI AEs in this subset of patients is presumed to be due to anastomotic dehiscence, a well-known complication of intestinal surgery in general and most commonly associated with colorectal anastomoses.[47-49] The risk of anastomotic leak in patients with advanced ovarian carcinoma and related gynecologic malignancies undergoing colorectal surgery may be a particular problem because of protein malnutrition that is common when these surgeries are performed before induction chemotherapy.[50] Results of a phase III trial reported by Vergote et al,[51] in which women with advanced ovarian cancer were randomly assigned to undergo primary debulking surgery before six cycles of postoperative chemotherapy or to undergo neoadjuvant chemotherapy (NACT) with interval debulking surgery after the third cycle of NACT, demonstrated that the rate of bowel resection at interval debulking surgery after NACT was approximately 50% lower (8.7% of 322 patients) than the rate at primary debulking surgery (15.5% of 310 patients).[51] The direct impact on this difference on the development of a GI AE as herein defined is unknown.

An important observation made in the current study is that not only were bevacizumab exposure and previous treatment of IBD and LBR at primary surgery independently associated with an increase in the odds of a GI AE, but also that in a logistic model there was no evidence that bevacizumab exacerbated the risk of a GI AE when these risk factors were present.

The interpretation of our data has additional limitations. First, several variables hypothetically associated with GI AEs were not specifically analyzed, including GI obstruction before treatment (an exclusion criterion for GOG 0218), protein malnutrition, specific chemotherapeutic regimen (identical across treatment groups), or bevacizumab dose density. Unfortunately we did not specifically examine laboratory indices of nutrition, such as pretreatment serum albumin. However, we found no association with PS, which may reflect nutritional state. Cytotoxic regimens including taxanes have been implicated, with mechanisms including necrosis of invasive tumor, bowel wall cytotoxicity, or transmigration of bacteria secondary to neutropenia.[52-55] The association of bevacizumab dose density with risk of GI AEs has been suggested in the meta-analysis by Hapani et al[29]; however, these were univariable analyses unadjusted for other factors such as type of combined chemotherapeutic agents. GOG 0218 utilized only one dose density for bevacizumab −5 mg/kg per week. The results of an open label phase III trial of bevacizumab in first-line therapy consisting of the same chemotherapy regimen utilized in GOG 0218 but with a bevacizumab dose density of 2.5 mg/kg per week demonstrated a similar frequency of GI AEs.[23] Thus far there is no evidence of a relationship to bevacizumab dose density in the management of patients with ovarian cancer.

Second, type I and type II statistical error could have influenced results and conclusions. Some positive findings could possibly be due to unadjusted multiple hypothesis testing. IBDs are rare conditions associated with development of GI perforation and fistula (particularly for Crohn disease).[56-58] In the current study, though a history of IBD or treatment thereof was reported in $< 1\%$ of the study population, those with a history of treatment for IBD had a 13-fold higher odds of a GI AE compared with those without such history.

The more concerning issue relates to negative findings where no statistically significant associations were found between biologically plausible risk factors and GI AEs. There are several possible explanations, including the relatively low number of events and the low frequency of some risk factors, creating imprecision in risk estimates.

Arguably, examples of this phenomenon may be on-study development of GI obstruction or complicated neutropenia, occurring in 39 (2.2%) and 86 (4.9%), respectively. Intestinal obstruction is a well-established risk factor for GI perforation[59] and has retrospectively been found to be a risk factor in a registry of approximately 2,000 patients with metastatic colorectal cancer treated with bevacizumab.[41] Severe neutropenia is thought to permit *trans*-mural invasion of pathogenic bacteria and has been implicated as a risk factor for enterocolonic perforation.[60]

Third, our results may not be completely applicable to other primary treatment scenarios, such as for patients with no macroscopic residual disease after initial surgery, receiving alternative regimens such as dose-dense paclitaxel with carboplatin,[61] treated with combined intraperitoneal-intravenous chemotherapy, or receiving induction NACT with interval surgical cytoreduction. Furthermore, the results may be even less applicable to those receiving bevacizumab with or without chemotherapy in the recurrent disease setting.

On the basis of our findings, we conclude that history of treatment for IBD and colon resection during initial surgery for advanced ovarian cancer appears to increase the risk of bowel perforation, fistula, necrosis, or bleeding during first-line platinum-taxane based treatment. After accounting for these risk factors, first-line treatment with bevacizumab also increases the odds of such a GI event, but bevacizumab does not appear to synergize with these other risk factors or increase the odds of GI AEs when it is continued after completion of platinum-taxane primary chemotherapy. Patients preparing for first-line therapy after surgery should be carefully counseled regarding the potential impact of these interventions and conditions on their individual risks.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Final approval of manuscript: All authors

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GLOSSARY TERMS

angiogenesis: the process involved in the generation of new blood vessels. Although this is a normal process that naturally occurs and is controlled by so-called on and off switches, blocking tumor angiogenesis (antiangiogenesis) disrupts the blood supply to tumors, thereby preventing tumor growth.

bevacizumab: also called Avastin (Genentech, South San Francisco, CA). Bevacizumab is a recombinant, humanized, monoclonal antibody that binds and neutralizes the vascular endothelial growth factor, thus acting as an antiangiogenic agent.

proportional hazards: semiparametric approach to survival analysis developed by Cox in 1972. Unlike product-limit (Kaplan-Meier) survival analyses, which are restricted to categorical predictor variables and do not produce a risk estimate, proportional hazards models can accommodate continuous and ordinal variables as well as allow for the inclusion of multiple predictor variables to compute adjusted risk estimates. Proportional hazards models are based on the fundamental premise that all individuals have the same baseline hazard that varies as a function of time [(t)], but that exposure to the independent variable changes the hazard by a fixed value [h(x)]. What is parameterized in the model is the value of this fixed effect per unit increase of the predictor variable whereas the value of (t) remains uncharacterized.

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Appendix

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