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Bevacizumab toxicities and their management in ovarian cancer

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Abstract

Objectives—The purpose of this review is to discuss the side effect profile of bevacizumab, to discuss proposed mechanisms of these toxicities, and to provide suggestions for management of adverse events.

Methods—A search of MEDLINE and ASCO and SGO abstract databases of articles published between January 1970 and August 2009 addressing the toxicity of bevacizumab in solid tumors was conducted. Reporting was limited to best available evidence including any available phase III studies and ovarian cancer phase II studies. Original publications addressing underlying mechanisms of bevacizumab toxicities were included.

Results—Extensive experience with bevacizumab has proven the agent to be generally well tolerated, with an adverse event profile distinct from traditional cytotoxic chemotherapy and likely peculiar to its novel mechanism of action. The most common bevacizumab-attributable adverse event, hypertension, can be medically-managed, but more serious adverse events such as bowel perforation require drug discontinuation.

Conclusions—Current best evidence supports the use of bevacizumab in selected patients, and safe administration of bevacizumab requires an understanding of the management of adverse events attributable to its use.

Keywords

Bevacizumab; Ovarian cancer; Toxicity

Introduction

Targeted and biologic therapies designed to augment the efficacy of traditional cytotoxic agents while minimizing adverse events are emerging as novel treatment options for solid tumor oncology. These therapies achieve antitumor activity through modulation of the cellular and molecular processes required for solid tumor growth, invasion, and metastasis. Among these, antiangiogenesis therapy is currently the best-studied and most effective biologic strategy for gynecologic cancers, and bevacizumab is the best-studied antiangio-

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

genesis agent to date. The purpose of this review is to discuss adverse events attributable to bevacizumab, their etiology and management. A search of MEDLINE, SGO and ASCO abstract databases was conducted. Search terms included: bevacizumab AND phase III, bevacizumab AND ovarian cancer, bevacizumab AND each side effect with a subheading in this article. Publications of phase III trials where bevacizumab was the only targeted, adjuvant therapy, of ovarian cancer phase II trials, and of possible mechanisms for adverse events were selected for reporting.

Bevacizumab

The immediate mechanism of action of bevacizumab is to bind and inactivate VEGF, thereby inhibiting endothelial, and possibly tumor, cell activation and proliferation [1]. Though the inhibition of tumor angiogenesis was originally thought to simply deny a tumor nutrients and oxygen, VEGF inhibition has also been shown to induce so-called vascular normalization, a restoration of normal structure, function, and flow to the disorganized, leaky vessels characteristic of malignant tumors, which improves the delivery of oxygen, nutrients, and cytotoxic chemotherapy to the tumor [2,3]. Because VEGF also plays an important role in normal physiologic processes – such as fetal development, stabilization of damaged endothelia, and wound healing – VEGF inhibition carries a unique toxicity profile that involves normal tissues, tumor tissues, and the interface of them. Despite uncertainty regarding these toxicities, the need for novel antitumor agents was an overriding force for the clinical investigation of bevacizumab.

Bevacizumab was first studied in patients with clear cell renal cell cancer, because of its unique VEGF-driven biology, and four other common solid tumors with high therapeutic need; namely, colon, prostate, lung, and breast cancers [4]. Phase III bevacizumab trials were warranted in metastatic colorectal cancer (mCRC) [5], metastatic non-small cell lung cancer (mNSCLC) [6], and metastatic breast cancer (mBC) [7], all of which met their primary endpoints, thus supporting FDA approval of bevacizumab for these indications. Recently, metastatic renal cell carcinoma (mRCC) [8] and glioblastoma multiforme [9,10] were added to this list, and one of the next opportunities for approval will be in epithelial ovarian and primary peritoneal carcinomas.

Efficacy of bevacizumab in ovarian cancer

The risks of bevacizumab therapy are best considered in the context of its efficacy. Five prospective phase II trials of bevacizumab in recurrent ovarian cancer have been conducted (Table 1): two single-agent trials [11,12], two in combination with cytotoxic chemotherapy [13,14], and one in combination with biologic chemotherapy [15]. The Gynecologic Oncology Group (GOG) conducted the largest single-agent study, GOG 170D, which reported a 21% overall response rate and a 40% 6-month progression-free rate in the 62 women, 66% of whom had received two prior regimens and 42% of whom were considered platinum-resistant [11]. A second single-agent, industry-sponsored trial conducted in an 84% platinum-resistant population – 48% of whom had received three prior regimens – reported an overall response rate of 15.9%, with 28% of patients progression-free at 6 months [12]. The two trials of bevacizumab combined with cytotoxic chemotherapy reported

response rates of 24% each and 6-month progression-free rates of 50% [13] and 56%, respectively [14]. There was also a trial of bevacizumab in combination with erlotinib, a biologic anti-epidermal growth factor receptor (anti-EGFR) agent, that reported a response rate of 15%, and the probability of being progression-free at 6 months was calculated at 38% [15].

All five clinical trials exceeded expectations for both response rate and proportion surviving progression-free at 6 months, generating enthusiasm for testing the addition of bevacizumab to carboplatin and paclitaxel for both frontline therapy and platinum-sensitive recurrences in several phase III trials summarized in Table 2 [16–19]. Accrual is complete for GOG 218 and ICON 7, but it remains ongoing for GOG 213 and OCEANS.

Overview of bevacizumab toxicity

Overall, bevacizumab is generally well tolerated. Its toxicities are usually nonoverlapping with those of cytotoxic chemotherapy, but may add to the AEs commonly seen with chemotherapy and, again, its vascular normalization properties are postulated to improve the efficacy of cytotoxics. The novel mechanism of action of bevacizumab is accordingly associated with a unique adverse event profile. The majority of adverse events are mild in severity and manageable, but some do result in significant morbidity and even mortality. In addition, some toxicities – such as bowel perforation in ovarian and mCRC, and pulmonary hemorrhage in squamous NSCLC – are seemingly disease site-dependent. Others – such as mucosal bleeding, hypertension, and proteinuria – are more nonspecific. Regardless, most adverse events likely result from the loss of VEGF activity that normally promotes physiologic, adaptive stabilization of malignant and nonmalignant blood flow.

The best measure of the incidence of toxicities due to bevacizumab is derived from published, randomized clinical trials in nonovarian disease sites, including mCRC, metastatic breast cancer, NSCLC, and renal cell carcinoma (Table 3) [5–8,20–24]. Table 4 lists the adverse effects with increased incidence of at least 2-fold in bevacizumab-treated patients over controls in these trials and that were included in the FDA-approved bevacizumab package insert [25]. Additionally, two phase IV, long-term bevacizumab safety studies, the Bevacizumab Regimens Investigation of Treatment Effects and Safety (BRiTE) study [26] and the Bevacizumab Expanded Access Trial (first BEAT) [27], were both designed to test the external validity of the efficacy and safety reported in the limited-access phase III trials by prospectively following community-based use of bevacizumab in mCRC. BRiTE, a US-based study, enrolled 1953 patients, 642 (33%) of whom were re-treated with bevacizumab after progression, providing a unique opportunity to determine the toxicity of repeated bevacizumab therapy. Prospective toxicity data in ovarian cancer with standardized reporting criteria are currently limited to six phase II trials: the five trials in recurrent disease that have been previously discussed and one in first-line therapy that has not yet been discussed [28].

The management of bevacizumab toxicity, in general, requires individualized decision-making that weighs drug efficacy against adverse event severity (grade) and potential long-term consequences of both the adverse event (s) and the disease. The goals of therapy

(palliative versus curative), potential alternative therapies, cost, and patient quality of life should all be factored into these decisions. Communicating to the patient the complexity of issues that inform treatment decisions can aid in the management of expectations as well. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [29] grading is most useful in the management of hypertension and proteinuria, because these adverse events develop gradually, and their mere occurrence does not indicate treatment discontinuation (Table 5). Although there is currently no established guideline for the management of toxicities due to bevacizumab, we summarize the current best evidence-based suggestions in Table 6. It should be noted that there is currently little role for dose reduction in the management of bevacizumab toxicity.

Hypertension

New-onset hypertension (HTN) and exacerbation of existing HTN are the most commonly reported adverse events attributable to bevacizumab. In randomized trials, the incidence of grade 3/4 HTN in bevacizumab-treated patients ranged from 3.0% to 14.8% compared with 0% to 2.0% for controls [5–8,20–24]. A meta-analysis of 1850 patients treated in seven randomized trials reported a statistically significant increase in the incidence of HTN that appeared to be dose-dependent (relative risk [RR]=3.0 for low dose, 95% CI, 2.2 to 4.2; RR=7.5 for high dose, 95% CI, 4.2 to 13.4) [30], but a randomized comparison of two different dose levels of bevacizumab showed no difference in grade 3/4 HTN between two groups [21]. Long-term follow-up studies reported grade 3/4 HTN in 5% of patients in the BEAT trial, while 19.4% of patients treated with any bevacizumab and 24.6% of those treated with long-term bevacizumab were reported in the BRiTE registry [26,27]. Rates of grade 3/4 HTN in ovarian cancer studies ranged from 4.5% to a high of 23% when bevacizumab was given in combination with sorafenib, another anti-VEGF therapy [11–15,28,31]. Wide variations in reported incidences of HTN might be explained by cross-trial differences in dosages and schedules of bevacizumab, the level of aggressiveness of anti-HTN treatment, whether there was pretreatment for HTN, the criteria used for defining HTN (though the randomized controlled trials used CTCAEs), and the stringency of reporting mandates (less stringent in phase IV studies).

Several potential mechanisms of HTN have been postulated. First, VEGF normally stimulates production of endothelial nitric oxide synthase (eNOS), an enzyme that catalyzes the conversion of oxygen and arginine to the potent vasodilator nitric oxide (NO). This VEGF inhibition results in lower levels of endogenous NO, vasoconstriction, increased peripheral vascular resistance, and thus higher blood pressure [32]. A second theory postulates an interaction of VEGF with angiotensin I and II receptors, inducing secretion of vasopressin and aldosterone, and thereby increasing blood pressure [32]. Finally, VEGF inhibition results in a functional decrease in the number of arterioles and capillaries in vascular beds, a phenomenon known as vascular rarefaction, which induces HTN by increasing systemic vascular resistance [33].

Treatment strategies for bevacizumab-related HTN have yet to be defined, but most traditional antihypertensives, including angioten-sin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, and diuretics, have successfully managed bevaci-

zumab-associated HTN. Rational, mechanism-based strategies include the use of vasodilatory nitrates that counteract reduced levels of endogenous NO and the effects of vascular rarefaction, angiotensin receptor blockers (ARBs) that compete with VEGF at the receptor level, and ACE inhibitors that have the added benefit of reducing the incidence of proteinuria, another possible adverse event of bevacizu-mab. None of these strategies has been investigated prospectively, however, and further studies are needed to establish the optimal antihypertensive therapy in bevacizumab-treated patients.

Blood pressure should be monitored regularly in patients receiving bevacizumab therapy. The GOG 218 protocol mandated blood pressure measurements prior to enrollment and prior to each cycle of bevacizumab or placebo. It also excluded the enrollment of women with uncontrolled HTN (systolic blood pressure >150 and diastolic blood pressure >90). Bevacizumab/placebo was held in cases of uncontrolled or symptomatic grade 3 or lower HTN until antihypertensive therapy resulted in controlled, asymptomatic grade 3 or lower HTN. If uncontrolled or symptomatic grade 3 HTN persisted or grade 4 HTN developed, bevacizumab/placebo was discontinued for the remainder of the study. Again, the majority of bevacizumab-related HTN events are mild in severity and can be managed medically without dose delay or treatment discontinuation.

Proteinuria

Urinary excretion of protein is commonly reported with bevacizumab administration, occurring in up to 63% of bevacizumab-treated patients [34]. Treatment-related proteinuria is typically mild in severity and non-dose-limiting, but it can rarely escalate to nephrotic syndrome. The incidence of grade 3/4 proteinuria in bevacizumab-containing arms of randomized trials was 0.8% to 4.0% compared to 0% to 1.0% in the control arms [5–8,20–24], and a meta-analysis of 1850 patients treated in seven randomized trials reported statistically significant relative risks of proteinuria equal to 1.4 with low-dose bevacizumab and 2.2 at higher doses [30].

The pathophysiology of bevacizumab-related proteinuria remains unknown, but it is postulated to result from a primary renal effect at the glomerular level. VEGF functions to maintain endothelial fenestrations that contribute to the glomerular filtration barrier. VEGF inhibition results in loss of fenestrations, endothelial edema, and detachment, as well as the loss of filtration barrier integrity, which is similar to the renal pathophysiology of preeclampsia [35]. Few reports of renal biopsies from patients experiencing grade 4 proteinuria have shown thrombotic microangiopathy or proliferative membranous glomerulonephritis, both of which might be direct results of the glomerular endothelial damage observed with VEGF inhibition [36]. Most proteinuria is typically reversible with the discontinuation of bevacizumab, but severe cases might remain persistent.

Patients receiving bevacizumab should be monitored for proteinuria prior to the initial and each subsequent dose of bevacizumab. Spot urinary protein levels alone inadequately reflect true excretion levels, but a calculated ratio of measured urinary protein and creatinine levels (UPCR) is an accurate monitoring method that is practical and economical. The UPCR has been shown to correlate with 24-hour levels of protein excretion, and a UPCR value of 1

approximates 1 g of proteinuria/24 h [37]. The GOG 218 and GOG 213 protocols exclude women with UPCR values >1 from enrollment, instruct withholding a bevacizumab cycle if UPCR values exceed 3.5, and mandate discontinuation if proteinuria persists beyond the treatment delay. Less conservative guidelines, however, might be followed when bevacizumab is used off-protocol. For example, an ACE inhibitor might be initiated in a patient who received clinical benefit from bevacizumab but has failed alternative treatment, instead of the discontinuation of bevacizumab called for in more conservative guidelines, especially if death from disease will likely precede significant renal failure.

Gastrointestinal perforation

Gastrointestinal perforation (GIP) has been reported in patients treated with bevacizumab for a variety of cancer primaries, but it has attracted substantial attention in ovarian cancer after leading to the premature closure of an important phase II trial in recurrent ovarian cancer [12]. Early mCRC randomized trials documented the increased but relatively low risk of GIP in bevacizumab-containing arms, with the resulting fatalities leading to the inclusion of GIP in the black box warning on the first package insert of bevacizumab in 2004 [38]. The incidence of GIP in bevacizumab-treated patients in randomized trials was 0% to 1.5% compared with <1% for controls [5–8,20–24], and a recent meta-analysis of 12,294 patients enrolled in 17 randomized trials reported an overall incidence of 0.9% (95% CI, 0.7% to 1.2%) with an increased relative risk of 2.14 (95%CI, 1.19 to 3.85, p=0.011) in the bevacizumab-treated groups [39]. The BRiTE study reported 34 GIPs (1.7%), most of which were not fatal, and the first BEAT documented 37 GIPs (2%) [26,27].

Soon after the FDA's initial approval of bevacizumab for mCRC and the inclusion of GIP in the package insert's black box warning, GOG 170D closed to accrual, reporting no GIPs [11]. Genentech subsequently activated AVF 2949 (N=44) in February 2005, and, by September, accrual was prematurely halted after the occurrence of five (11%) GIP events and one GIP-related death [12]. The investigators of the AVF 2949 trial performed an unplanned, retrospective subset analysis of potential factors associated with GIP, including bowel involvement, obstruction, distention or wall thickening on imaging, and three versus two prior regimens. The only statistically significant association identified was the receipt of three prior regimens. These findings prompted the FDA to issue an investigational new drug (IND) action letter dated October 4, 2005, reporting the GIP risk associated with bevacizumab in ovarian cancer patients. Protocol development for the four randomized trials listed in Table 2 continued because the majority of bevacizumab trials in ovarian cancer reported GIP rates lower than those in AVF 2949, plus heavily pretreated patients thought to be most at risk were not eligible for these trials. The best risk assessment for bevacizumab-related GIP and its associated mortality in ovarian cancer patients will be derived from the randomized trials listed in Table 2, although these results will only apply to a seemingly low-risk group that met criteria for enrollment for trials in first- and second-line therapies.

The mechanism by which bevacizumab contributes to GIP remains elusive, but it is most likely related to the anti-VEGF effects on bowel perfusion and/or tumor regression. Proposed mechanisms include intestinal wall disruption in areas of tumor necrosis, impaired

healing of pathologic or surgical bowel injury, and mesenteric thrombosis and/or vasoconstriction [40].

Though the incidence of GIP in bevacizumab-treated patients remains low, it is associated with a relatively high mortality rate. In the aforementioned meta-analysis of nonovarian patients, GIP was associated with a mortality rate of 21.7% [39]. Two reports of bevacizumab-associated GIPs were presented at the 39th Annual Meeting of the Society of Gynecologic Oncologists in 2009 [41,42]. These authors reported GIP in 9% (10/113) and 5.6% (6/107) of women, with 30-day mortality rates of 50% and 66%, respectively, which were entirely attributable to the GIP event. GIP occurred following a wide range of bevacizumab cycles (0.5 to 25) and cumulative doses (430 to 54,653 mg). Only rectovaginal nodularity was identified as a clinical risk factor predictive of GIP [47]. The high mortality rate of GIP in ovarian cancer is likely not only a reflection of the mortality of the GIP event itself but also of the patient's overall performance status and prognosis. Indeed, many patients receiving bevacizumab therapy have been heavily pretreated, have carcinomatosis and baseline bowel dysfunction, and would not benefit from, or even survive, reparative surgery in the instance of a treatment-related GIP event.

The identification of clinical risk factors for bevacizumab-related GIP would help minimize the incidence of this adverse event. The majority of GIP events reported in the BRiTE study occurred in patients with at least one of the following characteristics: acute diverticulitis, intra-abdominal abscess, GI obstruction, tumor at the GIP site, carcinomatosis, or prior radiation therapy [43].

Any patient treated with bevacizumab should be considered at risk for GIP, and early detection might help reduce the morbidity and mortality of this complication. Any patient experiencing new-onset abdominal pain should be evaluated for GIP; this evaluation should include a complete clinical history, a physical examination, and imaging. Patients with confirmed or highly suspected GIP whose overall condition is unstable secondary to the GIP should be considered for immediate surgical repair or diversion. Those who are more stable can be considered for less invasive management strategies such as bowel rest and broad-spectrum antibiotics with or without percutaneous drainage of concurrent abscesses. Acute patient condition, quality of life, and overall prognosis should be important factors in the decision to explore these patients surgically.

Thromboembolic events/hemorrhage

The rates of both arterial thromboembolism and hemorrhage are increased in patients receiving bevacizumab therapy. The reasons for this paradox are unclear, but coexistence of these effects suggests an indirect mechanism of VEGF inhibition. Under normal conditions, VEGF mediates the repair of endothelial surfaces that have sustained damage secondary to cardiovascular disease and other microangiopathies [44]. This results in exposed subendothelial tissues that initiate the clotting cascade and subsequent clot formation. The underlying prothrombotic state characteristic of cancer patients might exacerbate this process. Though somewhat counterintuitive, the mechanism leading to hemorrhage might

also result from a lack of endothelial repair in areas where subendothelial tissues are violated by pathophysiologic processes that may or may not be related to the malignancy.

Venous thromboembolism (VTE) has been reported in nearly all bevacizumab trials, but it is unclear whether bevacizumab increases the risk of VTE over the baseline increase associated with malignancy. Randomized trials reported VTE incidence rates in bevacizumab-treated patients that were not statistically different from those seen in controls [5–8,20–24], and two meta-analyses have reported both equivalent [45] and increased risk (RR=1.33, $p<0.001$) of VTE in bevacizumab-treated patients [46]. The incidence of VTE in phase II ovarian studies was relatively low (2% to 3%) [11–15,28], and patients with VTE, even pulmonary emboli, were not excluded from enrollment in GOG 218, provided therapeutic anticoagulation therapy had been established.

The incidence of arterial thromboembolic (ATE) events – including transient ischemic attacks, cerebral infarction, unstable angina, troponin elevation, and acute myocardial infarction – has been reported to be slightly, although statistically significantly, higher in bevacizumab-treated patients over controls, rarely resulting in fatal outcome. Randomized studies reported this difference as 4.4% compared with 1.9% [5–8,20–24], and a meta-analysis of 1745 nonovarian patients treated with bevacizumab reported an absolute number of 5.5 ATEs per 100 person-years, with a relative risk for ATE with bevacizumab of 2 ($p=0.03$) [45]. Risk factors for ATE identified in this analysis included age≥65 years, male sex, and history of ATE. Ovarian cancer studies reported similarly low incidences of ATE (0% to 3%) [11–15,28], some of which were particularly serious, including atrial thrombus resulting in pulmonary HTN [14]. Rates of ATE events were not increased with the addition of other anti-VEGF therapy to bevacizumab, but, again, this was in a small sample size [31].

All patients on bevacizumab should be considered at risk for ATEs, and extra caution should be exercised when prescribing bevacizumab to those >65 years old with a history of ATE or conditions which predispose them to ATE. Bevacizumab should be considered at least partially responsible for any ATE that occurs during treatment. There is no modification, aside from discontinuation of therapy, known to be more effective than standard medical treatment for bevacizumab-associated ATE events. As with all bevacizumab-related adverse events, the continuation of bevacizumab in specific situations in which bevacizumab benefit was either greater than the severity of toxicity or underlying predisposing factors were reversible (e.g., cardiac revascularization) might be considered, though overall prognosis might preclude such risks.

Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) is a neurological disorder that has been reported in association with HTN, eclampsia, and various states of immunosuppression due to organ transplant, chemotherapy, or autoimmune disorders. While it remains rare, RPLS has been increasingly reported with bevacizumab use, and this adverse effect was added, in 2006, to the prescribing information of bevacizumab in the “warnings and precautions” section [25].

The mechanistic link between bevacizumab and RPLS is unknown, but RPLS not associated with bevacizumab involves loss of cerebral vascular autoregulation, disruption of the cerebral tissue/capillary interface (blood–brain barrier), and vasogenic edema. These pathophysiologic states are common to proposed mechanisms for HTN and proteinuria, which were previously discussed in this paper. RPLS can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances, which can occur at any interval following bevacizumab administration. A high index of suspicion and documentation of posterior leukoencephalopathy on magnetic resonance imaging (MRI) are necessary to confirm the diagnosis. There is no specific treatment for RPLS outside of confirming the diagnosis, providing supportive care, which includes aggressive management of HTN, and discontinuing bevacizumab therapy. Again, in select cases in which a patient was receiving clinical benefit from bevacizumab, other therapeutic options have been exhausted, and the RPLS was mild and readily reversible, consideration for the resumption of bevacizumab administration is reasonable for the cooperative patient under close medical supervision.

Wound-healing complications/fistula

The disruption of wound healing, including delay, dehiscence, fistula, and abscess, has been reported with bevacizumab administration. Because of the long estimated half-life of bevacizumab (~20 days), the risk of wound-healing complications may persist even after its discontinuation. A pooled analysis of two randomized mCRC trials found no difference in the rate of wound-healing complications in bevacizumab-treated patients and controls, when bevacizumab was given at least 28 days following major surgery. The analysis, however, did report 10 wound-healing complications in 75 patients who underwent major surgery while on bevacizumab (13%) compared with 1 in 29 (3.4%) in controls [48]. The NSABP C08 randomized trial reported wound-healing complication rates of 1.7% in bevacizumab-treated patients compared with 0.3% in controls in the adjuvant setting following bowel resection for CRC [20]. Furthermore, specific wound-healing complications recorded included abdominal wound and port-site dehiscences but not anastomotic leaks. GOG 218 and ICON 7 are expected to provide similar data in ovarian cancer patients. In the BRiTE registry, 622 patients had surgery after starting bevacizumab therapy; 23 (3.7%) wound-healing complications were reported, occurring more often in patients undergoing major abdominal surgeries <60 days following the last bevacizumab dose [48]. Several of these patients had other predisposing factors to wound-healing impairment, such as infection, tumor involvement at the operative site, history of diabetes, and obesity.

Wound-healing complications were not increased in women in ovarian cancer trials; however, most participants were not surgical candidates [11–15]. The GOG 218 protocol delayed the administration of bevacizumab or placebo until the second cycle of chemotherapy, regardless of the timing of PDS. The optimal interval between the last bevacizumab dose administered and subsequent major surgery is generally considered to be the 60 days reported in the BRiTE registry [48] and the Scappaticci paper [47].

Fistula formation has been reported with bevacizumab use in ovarian cancer, but these are infrequent adverse events. One enterovaginal fistula was reported in the Garcia trial [14].

Though no management guidelines are available, fistula formation and wound disruption significant to result in major morbidity or impaired quality of life call for discontinuation of bevacizumab in most cases. The consequences of re-initiating bevacizumab in patients with wound disruption following healing remain unknown.

Conclusions

In summary, bevacizumab is the first biologic therapy targeted at tumor pathophysiology to show significant activity in ovarian cancer with acceptable added toxicity. The adverse events associated with bevacizumab, however, are specific to its biologic effects and are potentially serious, even fatal. Bevacizumab is currently listed as an active treatment for recurrent ovarian and primary peritoneal cancers by the National Comprehensive Cancer Network, but it is not yet FDA-approved for these indications. The administration of bevacizumab requires disclosure of the risks of, the benefits of, and alternative therapies to patients in an informed consent-like process. It is the opinion of the authors that the benefits of bevacizumab therapy, including quality of life, currently outweigh potential risks in most patients. Forthcoming results of phase III trials will confirm or refute this conclusion.

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Table 1

Prospective studies of bevacizumab efficacy in recurrent ovarian cancer.

	GOG 170D[11]	AVF 2797[12]	Chicago, CA, and PMH[14]	Chicago, CA and PMH[15]	Seattle[13],[a]
Number assessable	62	44	70	13	33
Platinum-sensitive, %	58	16		46	0
Platinum-resistant, %	42	84		54	100
Prior regimens, %					
1	34	–	–	8	NR[b]
2	66	52	100	62	
3	–	48	–	30	
Treatment plan	Bevacizumab 15 mg/kg q3w	Bevacizumab 15 mg/kg q3w	Bevacizumab 10 mg/kg q2w Cyclophosphamide 50 mg/d	Bevacizumab 15 mg/kg q3w Erlotinib 150 mg po qd	Bevacizumab 10 mg/kg q2w Topotecan 4 mg/m^2 qw of 28 day cycle
PFS at 6 months	40	28	56	38	50
Response rate, %					
CR	0	3	0	7.5	0
PR	18	16	24	7.5	24

PFS=progression-free survival, CR=complete response, PR=partial response, GOG=Gynecologic Oncology Group, PMH=Princess Margaret Hospital; CA=California.

[a] Accrual incomplete, trial-to-date data presented at the 2009 Society of Gynecologic Oncologists meeting.

[b] NR=not reported, maximum of 2 prior regimens allowed.

Table 2

Pivotal randomized clinical trials evaluating bevacizumab in ovarian cancer.

Study	Trial design	Status (as of July 2009)
First-line adjuvant therapy		
GOG 218 [16]	Randomized, placebo-controlled, three-arm, CT±bev with 18-cycle bev maintenance	Completed accrual June 2009
ICON-7 [17]	Randomized, two-arm, CT±bev with 12-cycle bev maintenance	Completed accrual February 2009
Second-line therapy		
GOG 213 [18]	Randomized, CT±bev	Open to accrual
OCEANS [19]	Randomized, placebo-controlled, CG±bev	Open to accrual

CT=carboplatin/paclitaxel, CG=carboplatin/gemcitabine, GOG=Gynecologic Oncology Group; ICON=International Collaborative Ovarian Neoplasm; bev=bevacizumab.

Table 3

Randomized phase III studies of bevacizumab in nonovarian cancers.

Author	Study	Disease site	*n*	Experimental arm	Bevacizumab dose/schedule
Allegra 2009[20]	NSABP C08	mCRC	2710	FOLFOX/bevacizumab	5 mg/kg q2w
Reck 2009[21]	AVAiL	NSCLC	1043	Cisplatin/gemcitabine/bevacizumab dose 1 Cisplatin/gemcitabine/bevacizumab dose 2	7.5 mg/kg q3w 15 mg/kg q3w
Saltz 2008[22]	XELOX-1/NO16996	mCRC	1401	XELOX or FOLFOX/bevacizumab	7.5 mg/kg q3w
Escudier 2008[8]	AVOREN	mRCC	649	IFN-alpha-2a/bevacizumab	10 mg/kg q2w
Miller 2007[7]	E2100	MBC	722	Weekly taxol/bevacizumab	10 mg/kg q2w
Giantonio 2007[23]	E3200	mCRC	829	FOLFOX/bevacizumab	10 mg/kg q2w
Sandler 2006[6]	E4599	NSCLC	878	Carboplatin/taxol/bevacizumab	15 mg/kg q 3w
Hurwitz 2004[5]		mCRC	923	IFL/bevacizumab	5 mg/kg q2w
Miller 2005[24]		MBC	462	Capecitabine/bevacizumab	15 mg/kg 13w

IFL=irinotecan, 5-fluorouracil and leucovorin; IFN=interferon; XELOX=oxaliplatin and capecitabine; FOLFOX=5-fluorouracil, oxaliplatin, and leucovorin.

Table 4

Adverse events associated with bevacizumab.

Adverse events		
Headache	Rhinitis	Rectal hemorrhage
Epistaxis	Taste alteration	Lacrimation disorder
Hypertension	Dry skin	
Proteinuria	Exfoliative dermatitis	
Warnings and precautions		
Nongastrointestinal fistula formation		
Arterial thromboembolic events (myocardial infarction, cerebrovascular accident)		
Hypertension (crisis or encephalopathy)		
Reversible posterior leukoencephalopathy syndrome		
Nephrotic syndrome		
Arterial thrombosis		
Infusion reactions		
Black box warnings		
Gastrointestinal perforation		
Surgical and wound-healing complications		
Hemorrhage		

Those that have increased at least 2-fold in bevacizumab-treated patients over controls in the trials listed in Table 2 and included in the FDA-approved bevacizumab package insert. The most common or concerning are in bold.

Table 5

National Cancer Institute common toxicity criteria of adverse events[34].

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension	Prehypertension (systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg)	Stage 1 hypertension (systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg); medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated.	Stage 2 hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Proteinuria	Urinary protein <1.0 g/24 h; UPCR <1	Urinary protein 1.0–3.5 g/24 h; UPCR 1–3.5	Urinary protein >3.5 g/24 h; UPCR >3.5	Nephrotic syndrome

BP=blood pressure; WNL=within normal limits; UPCR=urine protein to creatinine ratio.

Table 6

Recommendations for the management of bevacizumab-associated toxicities.

Hypertension	Grade 1	Monitor weekly, continue bevacizumab
	Grade 2	Initiate antihypertensive therapy; hold bevacizumab if hypertension is symptomatic
	Grade 3	Escalate antihypertensive therapy (increase dose of single-agent or add agent); hold bevacizumab until hypertension is asymptomatic grade 2
	Grade 4	Permanently discontinue bevacizumab
Proteinuria	Grade 1	Monitor every 3 weeks, continue bevacizumab
	Grade 2	
	Grade 3	Hold bevacizumab until proteinuria resolves to grade 2; consider angiotensin-converting enzyme inhibitor in consultation with internal medicine or nephrology
	Grade 4	Permanently discontinue bevacizumab
Gastrointestinal perforation		Maintain high index of suspicion when abdominal pain or obstructive symptoms occur; bowel rest and prompt evaluation with water-soluble contrast imaging. If patient has reasonable cancer prognosis and performance status, consider surgical repair. If prognosis and/or performance status are poor, risk of surgery might outweigh benefit. Manage coexisting abscess with systemic antibiotics±drainage (open or percutaneous). Permanently discontinue bevacizumab.
Arterial thromboembolism (transient ischemic attack, cerebrovascular infarction, unstable angina, troponin elevation, myocardial infarction)		Administer bevacizumab with caution in patient >65 years of age and/or with personal history of any arterial thromboembolism. Educate patients on warning signs and encourage prompt emergent care. Consult appropriate specialists (e.g., cardiology, neurology) to guide evaluation and management. Supportive care. Permanently discontinue bevacizumab.
Venous thromboembolism (deep vein thrombosis, pulmonary embolus)		Hold bevacizumab therapy until therapeutic anticoagulation established. Consider discontinuation of bevacizumab for complicated venous thromboembolism (failed adequate anticoagulation, respiratory compromise)
Reversible posterior leukoencephalopathy syndrome (RPLS)		Follow hypertension management suggestions. Maintain awareness of signs/symptoms of RPLS. Initiate prompt supportive care/management of hypertension. Permanently discontinue bevacizumab.
Wound-healing complications		Delay initiation of bevacizumab until 28 days following major surgery or until wound healing nearly complete. Delay major surgery, if possible, until 4 to 6 weeks following last dose of bevacizumab. Intravenous or intraperitoneal port placement and removal, endoscopic stenting, thoracentesis and paracentesis are not considered major procedures. Permanently discontinue bevacizumab in cases of fascial dehiscence.
Bleeding/hemorrhage		Use bevacizumab with caution in patients with vaginal and/or rectal metastases. Avoid bevacizumab use in patients with hemoptysis. Monitor minor bleeding (epistaxis, vaginal bleeding) with patient reporting, physical examination, and serial hemoglobin measurements. Permanently discontinue bevacizumab for bleeding events requiring acute transfusion resuscitation and/or interventional therapy (packing, surgery, embolization) to achieve hemostasis.