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Management of toxicity in patients receiving therapy with bevacizumab

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ABSTRACT

Bevacizumab has been administered to more than 200,000 cancer patients globally. This wealth of information has demonstrated that bevacizumab-associated adverse events are similar across indications. Commonly reported events with bevacizumab are hypertension (in up to 34% of patients), proteinuria (in up to 38% of patients) and haemorrhage (mucocutaneous haemorrhage in 20–40% of patients), most of which are grade 1–2 in severity. Less frequent events include arterial and venous thromboembolic events (ATEs, VTEs), congestive heart failure/cardiomyopathy, wound-healing complications and gastrointestinal perforations. These bevacizumab-associated events have also been reported in two phase III trials of bevacizumab in combination with chemotherapy (capecitabine [AVF2119g] or paclitaxel [E2100]) in advanced breast cancer. Overall, these adverse events are not dose-related in any indication (except for hypertension and grade 1 proteinuria). Furthermore, the most frequently reported bevacizumab-associated adverse events are mild/moderate in severity and are easily managed. Recommendations for the management of bevacizumab-related adverse events include regular monitoring (hypertension, proteinuria); use of standard care (hypertension, VTEs); temporary dose interruption (hypertension, proteinuria, VTEs, wound healing) to permanent discontinuation of treatment (for all severe events).

1. Introduction

Large phase III trials have demonstrated significant clinical benefits of bevacizumab in combination with standard chemotherapy in: metastatic colorectal cancer (first- and second-line),[1,2] non-small cell lung cancer (first-line),[3] renal cell cancer (first-line),[4] and metastatic breast cancer (first-line).[5] As such, bevacizumab is the first anti-angiogenic agent to have shown significant effects in patients with these common tumour types.

Bevacizumab has been administered to more than 200,000 cancer patients worldwide as part of a large clinical trial programme. Data from these trials indicate that bevacizumab has a similar safety profile across indications. Overall, bevacizumab is well tolerated. Most adverse events associated with bevacizumab do not appear to be dose-related, with some exceptions. In general, the most frequently reported bevacizumab-associated adverse events are mild or moderate in severity and easily managed.

This article reviews the range and extent of adverse events that can occur with bevacizumab, and provides recommendations for their management in patients with breast cancer.

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Table 1 – Grade 3/4 adverse events reported in a phase I/II trial of single-agent bevacizumab in metastatic breast cancer [6]

Adverse event	Incidence, n (%)			
	Bevacizumab 3 mg/kg ($n=18$)	Bevacizumab 10 mg/kg ($n=41$)	Bevacizumab 20 mg/kg ($n=16$)	Total ($n=75$)
Asthenia	1 (5.6)	4 (9.8)	2 (12.5)	7 (9.3)
Pain	1 (5.6)	2 (4.9)	1 (6.3)	4 (5.3)
Headache	1 (5.6)	1 (2.4)	3 (18.8)	5 (6.7)
Hypertension	4 (22.2)	7 (17.1)	3 (18.8)	14 (18.7)
Diarrhoea	0	0	1 (6.3)	1 (1.3)
Myalgia	0	3 (7.3)	0	3 (4.0)
Arthralgia	1 (5.6)	2 (4.9)	0	3 (4.0)
Cough increased	0	0	1 (6.3)	1 (1.3)
Dyspnoea	1 (5.6)	5 (12.2)	2 (12.5)	8 (10.7)
Proteinuria	1 (5.6)	1 (2.4)	1 (6.3)	3 (4.0)
Congestive heart failure	0	1 (2.4)	1 (6.3)	2 (2.7)

2. Single-agent bevacizumab in metastatic breast cancer

A phase I/II trial assessed the safety and efficacy of bevacizumab (3, 10 or 20 mg/kg every 2 weeks) in patients with previously treated metastatic breast cancer ($n=75$), to select a dose for further testing in this indication. [6] Patients received therapy with bevacizumab for a median of 70 days. Several grade 3/4 adverse events were noted, including hypertension, proteinuria, congestive heart failure (CHF)/cardiomyopathy, and headache (Table 1). Hypertension was reported most frequently, however, there was no relationship to bevacizumab dose, as grade 3/4 hypertension occurred in 22%, 17% and 19% of patients in the 3, 10 and 20 mg/kg groups, respectively. This observation is unusual, as clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. [7] Three patients experienced significant proteinuria (one at each dose level), two of whom developed nephrotic syndrome. A dose-limiting toxicity observed with bevacizumab was migraine-like headache, occurring in four patients (25%) at the 20 mg/kg dose. These headaches were of unknown aetiology, not being associated with hypertension or brain metastases, and responded well to treatment with dexamethasone.

Only four patients discontinued the study due to adverse events: one case each of hypertensive encephalopathy and proteinuria in the 10 mg/kg dose group, and one case each of nephrotic syndrome and severe headache in the 20 mg/kg dose group. [6] Bevacizumab was well tolerated, overall. In light of the dose-limiting toxicity at 20 mg/kg, a bevacizumab dose of 10 mg/kg every 2 weeks, or its equivalent of 15 mg/kg every 3 weeks, was selected for use in further metastatic breast cancer trials.

3. Adverse events of special interest in patients treated with bevacizumab

The expanding clinical trial programme with bevacizumab began to identify certain adverse events that are of special interest when using anti-angiogenic agents. The most commonly reported of these are hypertension, proteinuria and haemorrhage. Less frequently reported events include arterial thromboembolism (ATE) and venous thromboembolism (VTE), CHF/cardiomyopathy, wound-healing complications, and gastrointestinal (GI) perforation.

The majority of these adverse events are not dose dependent with regards to bevacizumab. [7] Further details of these toxicities are provided below, including potential mechanisms whereby anti-vascular endothelial growth factor (VEGF) agents may cause such events, any known risk factors, and recommendations for management. The incidence of bevacizumab-associated toxicity in two key phase III trials of bevacizumab with chemotherapy in advanced breast cancer is also described (Table 2). Trial E2100 investigated paclitaxel versus paclitaxel plus bevacizumab (10 mg/kg every 2 weeks) in 722 patients with first-line metastatic breast cancer. [5] In study AVF2119g, the addition of bevacizumab (15 mg/kg every 3 weeks) to capecitabine was compared with capecitabine alone in 462 patients with heavily pretreated metastatic breast cancer. [8] Data from study MO19391 (Table 2), an ongoing, open-label safety study of bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) plus taxane monotherapy or combination regimens as first-line treatment of metastatic breast cancer are also discussed. Preliminary data were presented at the 14th European Cancer Congress in 2007 and included a safety data group of 230 patients. [9]

Table 2 – Large clinical trials of bevacizumab plus chemotherapy in metastatic breast cancer

Trial number	Description	Efficacy outcomes
E2100 [5]	Multicentre, randomised phase III trial of first-line paclitaxel with or without bevacizumab in locally recurrent or metastatic breast cancer ($n = 722$)	The addition of bevacizumab to paclitaxel significantly increased median progression-free survival (11.4 vs. 5.8 months, $p < 0.0001$) response rate (48% vs. 23.4%, $p < 0.0001$) and 1-year survival (81.4% vs. 74.0%, $p = 0.017$)
AVF2119g [8]	Multicentre, randomised phase III trial of capecitabine with or without bevacizumab in previously treated metastatic breast cancer ($n = 462$)	The addition of bevacizumab to capecitabine significantly increased response rate (30.2% vs. 19.1%, $p = 0.006$), but not progression-free survival or overall survival
MO19391 [9]	Multicentre, single-arm safety study of first-line taxane-based chemotherapy plus bevacizumab in locally recurrent or metastatic breast cancer. Choice of chemotherapy regimen is at the discretion of the investigator; if taxanes are contraindicated, or not standard of care of the investigator, the investigator's standard of care regimen may be used. Anthracyclines, however, are not permitted ($n \approx 2{,}300$)	No efficacy data are yet available for this trial

Direct comparisons between the three trials are difficult due to differences in patient populations, exposure to prior therapy, and chemotherapy regimen used. A particular issue with the collection of data from the E2100 study is also noteworthy. Expedited reporting of adverse events was conducted through the National Cancer Institute Adverse Event Expedited Reporting System (NCI Adeers) for patients in the bevacizumab plus paclitaxel arm and not mandated in those receiving paclitaxel alone.

4. Commonly reported events with bevacizumab

4.1. *Hypertension*

Several class-effect mechanisms have been hypothesised by which agents targeted against VEGF may cause hypertension. [10] VEGF is known to increase the synthesis of nitric oxide, a vasodilator, through upregulation of endothelial nitric oxide synthase. [11] Anti-VEGF agents therefore decrease levels of endogenous nitric oxide in blood vessel walls, resulting in vasoconstriction and increased blood pressure. This effect may be exacerbated by a related increase in the expression of plasminogen activator inhibitor-1 (PAI-1), which is involved in regulating endogenous fibrinolytic activity and resistance to thrombolysis. [12] A reduction in vascular density in response to anti-VEGF agents may lead to an overall increase in vascular resistance. Furthermore, anti-VEGF-induced reduction in vascular permeability may increase intravascular blood volume.

The clinical efficacy of agents that inhibit epidermal growth factor receptor (EGFR) is known to be associated with the severity of the skin toxicity that arises during treatment. [13] Indeed, one randomised phase I/II trial of cetuximab in patients with metastatic colorectal cancer demonstrated that escalating the dose of this agent in patients with no, or mild, skin rash increased the response rate. [14] It has been suggested that a similar relationship may exist between hypertension and clinical efficacy in patients treated with bevacizumab. In a phase II trial of bevacizumab plus gemcitabine in pancreatic cancer, patients with early hypertension (defined as grade >2 hypertension within 56 days of therapy initiation, $n = 6$) demonstrated a trend towards longer median overall survival than those without early hypertension ($n = 40$; 13.7 vs. 8.7 months; $p = 0.067$). [15] If there is a correlation, patient outcomes could potentially be improved by increasing bevacizumab dose according to blood pressure measurements, thereby identifying the optimal biological dose for each patient. Further analyses evaluating this potential correlation are warranted in ongoing randomised phase III studies to understand whether hypertension may be a predictive factor for bevacizumab efficacy.

The National Cancer Institute–Common Terminology Criteria for adverse events (NCI-CTCAE), version 3, defines hypertension as a blood pressure increase by >20 mmHg diastolic or to >150/100 if previously normal. [16] NCI-CTCAE grades of hypertension are detailed in Table 3.

Bevacizumab was associated with the development of hypertension in both phase III metastatic breast cancer trials (Figure 1). Non-haematological adverse events of grades 1 and 2 were not recorded in trial E2100. In this trial, the incidence of grade 3 and 4 hypertension in the bevacizumab plus paclitaxel group was 15.4% and 0.6%, respectively, compared with 1.4% and 0%, respectively, for the paclitaxel group. [17] Grade 4 hypertension was not observed in the AVF2119g trial, but the incidence of grade 3 hypertension was 0.5% for the capecitabine group versus 17.9% for the capecitabine plus bevacizumab group. [8] Grade 3 hypertension was reported in 0.9% of

Table 3 – NCI-CTCAE version 3.0 grades of commonly reported bevacizumab-associated adverse events [16]

Adverse event	Definition		
Hypertension			
Grade 1	Asymptomatic, transient increase; no treatment required		
Grade 2	Recurrent, persistent or symptomatic increase; monotherapy may be required		
Grade 3	Requiring more than one drug or more intensive therapy than previously		
Grade 4	Life-threatening (e.g. hypertensive crisis)		
Proteinuria		Dipstick	Urine protein level
Grade 1	Transient	1+	0.15–1.0 g/24 hours
Grade 2	Persistent moderate	2+ to 3+	>1.0–3.5 g/24 hours
Grade 3	Severe	4+	>3.0 g/24 hours
Grade 4	Nephrotic syndrome	As above, with hypoalbuminaemia and peripheral oedema	
Bleeding			
Grade 1	Mild, intervention not indicated		
Grade 2	Symptomatic, medical intervention indicated		
Grade 3	Transfusion indicated		
Grade 4	Life-threatening consequences, major urgent intervention indicated		

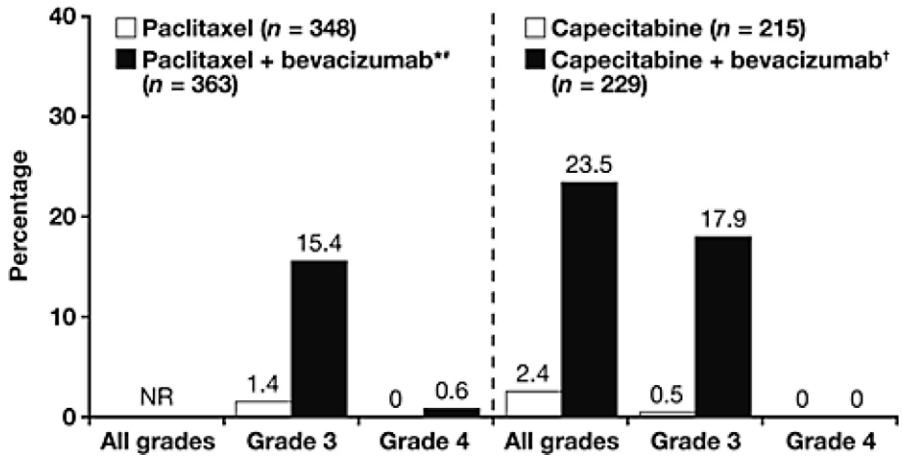

Fig. 1 – Incidence of hypertension in phase III trials of bevacizumab in metastatic breast cancer. [8,17] *Bevacizumab given every 2 weeks; †Bevacizumab given every 3 weeks. #Includes NCI AdEERS mandatory collection in the paclitaxel plus bevacizumab arm only, which does not allow valid comparison between the two arms. NR = not reported.

patients in the MO19391 study, with no reports of grade 4 hypertension. [9]

High blood pressure should be managed actively and several recommendations have been made in relation to bevacizumab-associated hypertension. [7] Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Routine blood pressure monitoring is recommended during bevacizumab therapy. In most cases, hypertension can be controlled adequately using standard antihypertensive treatment (e.g. angiotensin-converting enzyme [ACE] inhibitors, diuretics, calcium channel blockers) appropriate for the individual patient. [12,18,19] Indeed, beta blockers and ACE inhibitors were the most commonly prescribed anti-hypertensive agents in a large community-based registry of patients with metastatic colorectal cancer receiving bevacizumab and chemotherapy. [19] Although no particular class of antihypertensive agent is recommended above others, it is speculated that ACE inhibitors may be a more logical choice due to their inhibition of PAI-1 expression. [12] Secondary effects of ACE inhibitors on renal podocytes may have the added benefit of decreasing bevacizumab-associated proteinuria. [12]

Caution should be exercised before starting bevacizumab therapy in patients with uncontrolled hypertension as there is no information on the effects of bevacizumab in this patient group. Temporary interruption of bevacizumab treatment should be considered for patients developing uncontrolled hypertension, until it is controlled. Permanent discontinuation of bevacizumab is required if medically significant hypertension cannot

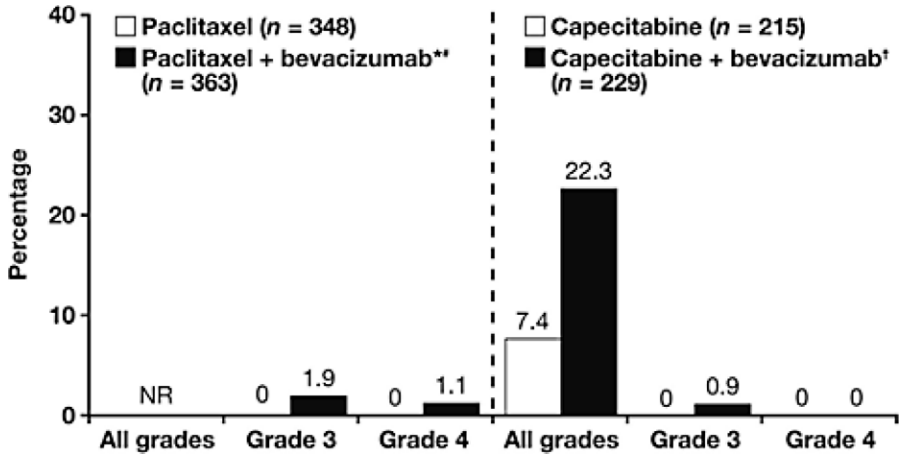

Fig. 2 – Incidence of proteinuria in phase III trials of bevacizumab in metastatic breast cancer. [8,17] ***Bevacizumab given every 2 weeks; †Bevacizumab given every 3 weeks. #Includes NCI AdEERS mandatory collection in the paclitaxel plus bevacizumab arm only, which does not allow valid comparison between the two arms. NR = not reported.**

be controlled with antihypertensives, or if hypertensive crisis or hypertensive encephalopathy occur. Discontinuation of bevacizumab is rarely necessary.

Reversible posterior leukoencephalopathy syndrome (RPLS)

RPLS is a rare neurological disorder. A very small number of patients treated with bevacizumab (<0.1%), [20] or other anti-VEGF compounds e.g. sunitinib and vatalanib [21–23] have developed RPLS. There does not appear to be any relationship between duration of exposure to an anti-VEGF agent and RPLS, as symptoms have first occurred from 16 hours to 1 year after initiation of bevacizumab therapy. [20] Symptoms include seizures, headaches, altered mental state and visual disturbance/cortical blindness with or without hypertension. The diagnosis of RPLS should be confirmed by MRI scan. Treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. [7] The safety of restarting bevacizumab in patients with previous RPLS is unknown.

4.2. *Proteinuria*

In the kidney, VEGF maintains the glomerular and peritubular capillary network. [24] Use of an anti-VEGF agent may therefore perturb this network of blood vessels, leading to glomerular dysfunction and proteinuria. Proteinuria is graded 1–4, according to the NCI-CTCAE, and based on dipstick and/or 24-hour urine collection results (Table 3).

Proteinuria, an established side effect of bevacizumab therapy, has been consistently reported in clinical trials of this agent with various chemotherapy regimens in several tumour types. [1,3,25,26] Figure 2 shows the incidence of proteinuria in the E2100 and AVF2119g advanced breast cancer trials. Chemotherapy alone did not lead to grade 3/4 proteinuria. A very low incidence of grade 3 and 4 proteinuria was noted in the bevacizumab plus paclitaxel (1.9%, 1.1%, respectively) and bevacizumab plus capecitabine (0.9%, 0%) groups. [8,17] Most of the reported proteinuria in trial AVF2119g was grade 1 and not associated with renal dysfunction. [8] A similarly low incidence of grade 4 proteinuria (0.4%) was reported in the MO19391 study. [9] Proteinuria is reversible, although the long-term sequelae (if any) are currently unknown.

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. [7] Proteinuria monitoring (dipstick analysis) is recommended prior to and during bevacizumab therapy – 24-hour urine collection should be used if the dipstick reading is $\geqslant$2+ (3+ on second and subsequent occurrences). Bevacizumab should be interrupted if urine protein levels are $\geqslant$2 g/24 hours and can be restarted once levels are <1 g/24 hours. Discontinuation of bevacizumab is rarely required, although it is suggested that treatment should be stopped in patients with nephrotic syndrome.

Both proteinuria and hypertension are observed in women who develop pre-eclampsia. Interestingly, recent evidence indicates that pre-eclampsia is associated with high circulating levels of soluble VEGF receptor (sFlt-1). [27] This produces low levels of free VEGF, a situation analogous to that found in bevacizumab-treated patients.

4.3. *Haemorrhage*

VEGF is a major factor regulating vascular endothelial cell mitogenesis. Disruption of this process by anti-VEGF agents may decrease the renewal capacity of endothelial cells in response to trauma. [28] Furthermore, endothelial dysfunction could occur, resulting in a defective internal vascular lining. Such events may eventually lead to

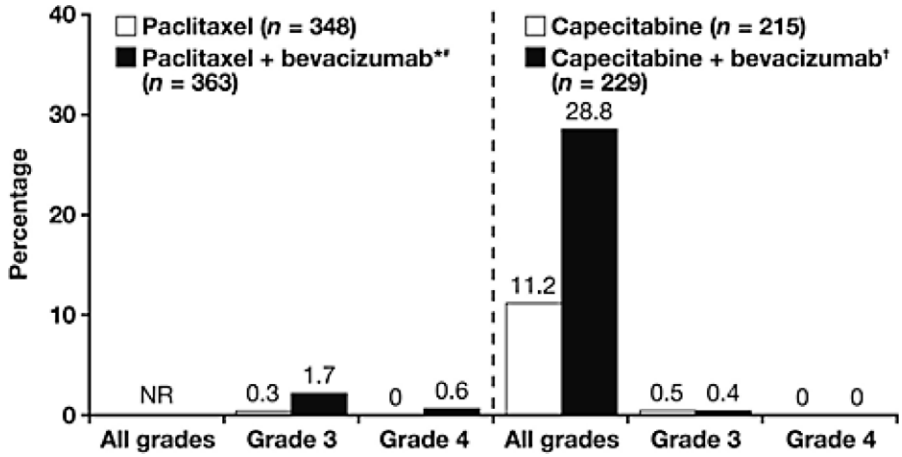

Fig. 3 – Incidence of bleeding events in phase III trials of bevacizumab in metastatic breast cancer.[8,17] *Bevacizumab given every 2 weeks; †Bevacizumab given every 3 weeks. #Includes NCI AdEERS mandatory collection in the paclitaxel plus bevacizumab arm only, which does not allow valid comparison between the two arms. NR = not reported.

bleeding. Table 3 describes the NCI-CTCAE definitions of grade 1–4 haemorrhage.

Clinical studies of bevacizumab in cancer patients have reported haemorrhagic events. These findings were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis).[10,29] Bleeding events also occurred in the phase III metastatic breast cancer trials of bevacizumab (Figure 3), although most of these were grade 1 or 2 in severity.[8,17] Grade 4 bleeding events were reported in two patients in the bevacizumab plus paclitaxel arm of the E2100 study. Both patients experienced central nervous system (CNS) haemorrhage, one diagnosed as a subdural haematoma sustained after a fall and the other within the setting of a grade 4 CNS ischaemic event. The most common bleeding event in bevacizumab trials in all indications is grade 1 nose bleed that does not require medical intervention.[7] Bevacizumab therapy must be permanently discontinued in patients who experience grade 3/4 bleeding.

In clinical trials of bevacizumab, patients with CNS metastases were excluded, thus, the risk of CNS haemorrhage with bevacizumab in such patients has not been fully evaluated. In the absence of safety data, bevacizumab should not be given to patients with CNS metastases.[7] It is noteworthy however, that experience with bevacizumab in the treatment of glioma is accumulating.

Patients receiving full-dose anticoagulant therapy or aspirin have historically been excluded from clinical trials of bevacizumab due to the concern regarding bleeding. However, two analyses of patients with metastatic colorectal cancer receiving chemotherapy showed that the incidence of haemorrhagic events was not increased with the concomitant use of bevacizumab and low-dose aspirin ($\leqslant$325 mg/day)[30] or full-dose anticoagulants.[31] More recent clinical trials of bevacizumab in patients with breast cancer have included patients receiving therapeutic anticoagulation.

5. Less frequently reported events with bevacizumab

5.1. *Arterial thromboembolic events*

ATEs, including cerebrovascular accidents, myocardial infarction, and transient ischaemic attacks are rare, although bevacizumab therapy has increased their incidence across indications. There were no reports of ATEs in the paclitaxel group of the E2100 study (Table 4). However, 13 patients (3.6%) in the paclitaxel plus bevacizumab arm had ATEs: four grade 3; seven grade 4; two grade 5.[17] These included nine cases of cerebrovascular ischaemia and four cases of cardiac ischaemia, two of which were grade 5. In contrast, the frequency of ATEs in the AVF2119g trial was similar in the capecitabine arm (0.5%) and the capecitabine plus bevacizumab arm (0.4%).[8] No ATEs were reported in trial MO19391.[9]

Several risk factors for ATEs have been identified across bevacizumab trials.[7,32] There is an increased risk of an ATE in bevacizumab-treated patients who have a prior history of stroke/heart attack (~5 fold), in those aged $\geqslant$65 years (~3 fold) and in patients with hypertension (~2 fold). Bevacizumab should be permanently discontinued in patients who develop ATEs.

5.2. *Venous thromboembolic events*

VTEs include deep venous thrombosis, pulmonary embolism and thrombophlebitis. Across indications, the overall incidence of VTEs ranged from 2.8–17.3% of bevacizumab-treated patients compared with 3.2–15.6% of controls.[7] It is unclear whether VTEs are due to the underlying cancer, chemotherapy, bevacizumab or other factors.

Table 4 – Less frequently reported grade ⩾3 adverse events in trials of bevacizumab plus chemotherapy in metastatic breast cancer

Adverse event, n (%)	E2100 [17]		AVF2119g [8]		MO193919 [9]
	Paclitaxel ($n = 348$)	Paclitaxel + bevacizumab ($n = 363$) [a]	Capecitabine ($n = 215$)	Capecitabine + bevacizumab ($n = 229$)	Chemotherapy + bevacizumab ($n = 230$)
Arterial thromboembolic events	0	13 (3.6)	1 (0.5)	1 (0.4)	0
Venous thromboembolic events	15 (4.3)	11 (3.0)	8 (3.7)	14 (6.1)	2 (0.9)
Congestive heart failure/cardiomyopathy	1 (0.3)	8 (2.2)	2 (1.0)	7 (3.1)	0
Wound-healing complications	0	4 (1.1)	0	0	0
Gastrointestinal perforations	0	2 (0.6)	0	0	0

[a] Includes NCI AdEERS mandatory collection in the paclitaxel plus bevacizumab arm only, which does not allow valid comparison between the two arms.

The incidences of grade 3/4 VTEs in the E2100 study were 4.3% (paclitaxel) and 3.0% (bevacizumab plus paclitaxel) (Table 4).[17] There was an apparent increase in grade 3/4 VTEs in the AVF2119g trial in the bevacizumab plus capecitabine arm (6.1%) compared with the capecitabine arm (3.7%).[8] In study MO19391, VTEs reported as serious adverse events occurred in 0.9% of patients.[9]

Patients who have had a VTE in the past may be at higher risk for recurrence if they receive bevacizumab combined with chemotherapy. However, patients who developed venous thrombosis whilst on bevacizumab did not appear to be at an increased risk of grade ⩾3 bleeding when anticoagulated.[31] If any grade 3/4 VTE occurs in a clinical trial, dosing with bevacizumab should be stopped for 3 weeks. Administration should only be continued when anticoagulation parameters have stabilised. Patients with symptomatic pulmonary embolism must not be treated with bevacizumab.

5.3. *Congestive heart failure/cardiomyopathy*

CHF has been observed with bevacizumab in a variety of cancer indications to date, although incidence may be increased in metastatic breast cancer patients. The incidence of grade 3–5 CHF was higher in patients treated with paclitaxel/bevacizumab (2.2%) compared with those receiving paclitaxel alone (0.3%) in the E2100 trial (Table 4).[17] In the AVF2119g study, grade 3/4 CHF and cardiomyopathy each occurred at an incidence of 0.5% in patients receiving capecitabine alone versus incidences of 2.2% and 0.9%, respectively, for those receiving combined capecitabine and bevacizumab.[8] Most affected patients showed improvement of symptoms or left ventricular function following appropriate medical therapy. There were no reported cases of CHF in the MO19391 study.[9]

The incidence and severity of CHF in breast cancer patients with a history of anthracycline exposure are known to increase with cumulative anthracycline dose and chest wall irradiation.[33] The AVF2119g trial confirmed these risk factors for CHF in patients treated with bevacizumab.[8] An exploratory analysis in trial E2100 demonstrated a 3.8% incidence of left ventricular dysfunction in patients (paclitaxel/bevacizumab) who had previously received anthracyclines.[17] Routine assessment of left ventricular ejection fraction is not usually recommended. If CHF occurs, bevacizumab therapy should be permanently discontinued.

5.4. *Wound-healing complications*

Angiogenesis is one critical mechanism in the complex process of wound healing[34] and bevacizumab, as an anti-angiogenic agent, has the potential to disrupt wound healing. In two randomised trials in metastatic colorectal cancer, wound-healing complications occurred in 13.0% of patients who underwent surgery while receiving bevacizumab plus chemotherapy, compared with 3.4% of patients who received chemotherapy alone.[35] The incidence of wound-healing complications dropped enormously, however, in patients whose surgery was performed 28–60 days prior to initiation of bevacizumab (1.3% vs 0.5% of control patients).[35] In a large, community-based safety study of bevacizumab in colorectal cancer (First BEAT), it was recommended that bevacizumab be discontinued a minimum of 6–8 weeks before elective surgery and restarted 28 days after the procedure.[36] Of 225 patients who underwent surgery with curative intent, three (1.3%) reported surgery-related wound-healing complications,[36] comparing favourably with previously reported rates of dehiscence in GI operations.[35] This suggests that wound-healing complications may affect a minority of patients who receive surgery during bevacizumab therapy, but that this risk declines considerably in patients who have a sufficient break in bevacizumab therapy surrounding the time of surgery.

Grade 3/4 wound-healing complications were noted in 1.1% of patients treated with paclitaxel plus bevacizumab in the E2100 study, but not in patients receiving paclitaxel alone (Table 4).[17] No such events were reported in the AVF2119g trial or the MO19391 trial.[8,9] The trials of bevacizumab in breast cancer have not thus far included patients who have had elective surgery in the recent past

as part of their cancer treatment. Ongoing studies in early-stage breast cancer will examine wound healing as a specific endpoint.

Since the half-life of bevacizumab is approximately 21 days,[37] it is recommended that therapy should not be initiated for at least 28 days following major surgery or until the wound is fully healed.[7] For those patients who experience wound-healing complications, bevacizumab should be withheld until the wound is fully healed. Furthermore, bevacizumab should be withheld 28–42 days before elective surgery,[35,38] although the optimal interval has still to be determined.

5.5. *Gastrointestinal perforations*

GI perforation, a potentially life-threatening condition, occurs infrequently with bevacizumab therapy.[7] Symptoms include abdominal pain, constipation and vomiting. In the E2100 trial, GI perforations were reported in two patients (grade 5, 0.6%) in the combined bevacizumab plus paclitaxel arm (Table 4).[17] There were no reported cases in the AVF2119g or MO19391 trials.[8,9]

The mechanism by which anti-VEGF therapy contributes to GI perforation is currently unknown, but there are likely to be a number of contributing factors. Many such perforations may be due to the shrinkage of tumour masses embedded in the intestinal wall, or may occur at the site of previous surgery.[10,39] Other risk factors include abscesses, diverticula or an inflammatory process involving the GI tract.[10,25] It is speculated that VEGF inhibition may hinder the repair of the GI tract after cytotoxic damage and that this may increase the chance of perforation occurring when coupled with further insult such as an infection or obstruction.[40]

In the two patients with GI perforation reported in the E2100 trial, one had diverticulitis and the other had tumour erosion of the bowel.[17] This apparent association with these underlying risk factors is consistent with GI perforation events in bevacizumab studies in patients with other tumour types receiving other chemotherapy-based regimens.[25,39] Thus, caution should be exercised when treating patients suffering from intra-abdominal inflammatory processes with bevacizumab, and it is recommended that therapy is permanently discontinued in any patient developing GI perforation.

A Sanofi-Aventis-sponsored phase II study of docetaxel, gemcitabine and bevacizumab in patients with locally advanced or metastatic non-small cell lung cancer was recently terminated due to an increased incidence of GI perforations, above the reported rate for each drug as a single agent. Databases of two bevacizumab safety studies, MO19391 (in first-line metastatic breast cancer) and MO19390 (a similar study in patients with non-small cell lung cancer), that include this combination therapy were subsequently examined, but the findings from the phase II lung study could not be reproduced. This was confirmed by the Data Safety Monitoring Boards of both studies.

6. Chemotherapy-associated adverse events

In addition to the adverse events described above, other toxicities occurred in both phase III metastatic breast cancer trials with bevacizumab and chemotherapy. Many of these additional events were typical chemotherapy-associated toxicities, and it cannot be clearly ascertained to what extent bevacizumab contributed to these findings. In the AVF2119g study, typical capecitabine-induced side effects were not further enhanced by the addition of bevacizumab.[8] However, in the E2100 trial, grade 3/4 paclitaxel-associated events were apparently increased by the addition of bevacizumab i.e. sensory neuropathy (24.2% vs. 17.5%), fatigue (10.7% vs. 5.2%) and neutropenia with or without infection (17.4% vs. 8.0%).[17] A likely explanation for the differences between the trials is the length of chemotherapy exposure. In the AVF2119g trial, no progression-free survival benefit was observed, so there was no difference in treatment duration between the arms.[8] In contrast, in the E2100 trial, the substantial improvement in progression-free survival was associated with longer paclitaxel treatment in the bevacizumab arm.[17] Hence, the apparent increase in chemotherapy-related toxicity is likely to be due to increased exposure to paclitaxel rather than the addition of bevacizumab.

7. Adverse events associated with other anti-VEGF inhibitors

Bevacizumab is a monoclonal antibody that selectively binds VEGF. Other anti-VEGF agents include small molecule tyrosine kinase inhibitors (TKIs), which target the receptors of VEGF and other growth factors. Some of the adverse events associated with bevacizumab also occur with other inhibitors of the VEGF pathway, such as sunitinib, sorafenib, and vatalanib, as outlined briefly below.

The most commonly reported adverse events (>20% patients) with sunitinib are hypertension (all grades: 30%; grade 3/4: 4–10%)[41,42] and mild bleeding (30%).[43] Rare events include RPLS (<1%), tumour-related haemorrhagic events, CHF (11–15% of patients with low left ventricular ejection fraction) and GI perforation. Typical anti-VEGF-related adverse events have also been reported for sorafenib. These include hypertension (all grades: 17%; grade 3/4 3%), haemorrhage/bleeding (15% [2% grade 3/4] vs. 8% placebo group), RPLS (rare), CHF (2.9% sorafenib vs. 0.4% placebo) and GI perforation (<1%).[44] Grade 3/4 adverse events associated with vatalanib in phase III colorectal cancer trials are hypertension (21% vs. 5% for placebo), ATEs (6% vs. 1% for placebo) and RPLS (1%).[45] Cediranib and axitinib are VEGF receptor TKIs that are currently under investigation in a variety of

tumours. In several preliminary trials abstracted to date, hypertension is a common anti-VEGF-related adverse event with these compounds [46–48]

These anti-VEGF TKIs are also associated with other adverse events that are not observed with bevacizumab use. For example, sunitinib and sorafenib induce dermatological toxicity such as rash and hand-foot syndrome. [43,44] Diarrhoea and severe fatigue are also commonly reported for sunitinib, sorafenib, vatalanib and cediranib. A possible explanation for such differences in the adverse event profiles between these TKIs and bevacizumab is the more promiscuous nature of the TKIs, as they inhibit receptors other than VEGF, including platelet-derived growth factor α/β, c-KIT and RET.

8. Conclusions

Extensive experience with bevacizumab in cancer patients indicates that this anti-angiogenic agent has a well-defined and manageable safety profile that is consistent across indications. The most common treatment-related adverse events are hypertension, proteinuria and haemorrhage/bleeding. Less frequent events include ATEs, VTEs, CHF/cardiomyopathy, wound-healing complications and GI perforations. Clinical data to date suggest that this safety profile extends to patients with breast cancer. Additional studies are ongoing to further evaluate the efficacy and safety of bevacizumab in all stages of breast cancer.

As bevacizumab is an anti-angiogenic agent, it is maybe not surprising that certain adverse events (e.g. hypertension, proteinuria, bleeding) occur based on the known role of angiogenesis and/or VEGF in the normal physiology of these processes. Indeed, some adverse events (e.g. hypertension, bleeding/haemorrhage, RPLS, ATEs, CHF and GI perforation) appear to be common to other therapies inhibiting the VEGF pathway.

The majority of adverse events can be successfully managed through the use of standard medical techniques. Regular monitoring is recommended for hypertension and proteinuria. Additional medication should be used to adequately control certain conditions, such as antihypertensive treatment for high blood pressure, and anticoagulants for VTEs. Temporary interruption of bevacizumab therapy is advisable in the event of uncontrolled hypertension, proteinuria, grade 3/4 VTEs or wound-healing complications. Discontinuation of bevacizumab is rarely required.

Data from clinical trials of bevacizumab in advanced breast cancer have shown that this agent prolongs disease stability and improves quality of life compared with chemotherapy alone. [5] Although the addition of this agent to a therapy regimen is associated with some novel adverse events, the majority of these are of low grade and most are easily managed. The benefits to patients resulting from the use of bevacizumab can therefore be seen to outweigh the additional toxicity produced. It is likely that this positive benefit:risk profile will also be seen in the treatment of early breast cancer, where the potential therapeutic gains are greater. Indeed, a pilot study of bevacizumab in the adjuvant setting recently demonstrated that this agent can be combined with an anthracycline-containing regimen with acceptable levels of cardiac toxicity. [49]

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Conflict of interest statement

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