Using bevacizumab to treat metastatic cancer: UK consensus guidelines

Concise guidance is lacking for the use of bevacizumab by practicing oncologists. Eight oncologists with experience of bevacizumab were joined by a cardiologist interested in treating hypertension to develop practical guidelines for managing patients receiving bevacizumab, using available clinical data.

Bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor (VEGF), acts on tumour vasculature to inhibit tumour growth and metastasis (Gerber, 2005). In Europe, bevacizumab is approved for use in combination with standard therapies for the treatment of metastatic breast cancer, colorectal cancer, renal cell carcinoma and non-squamous non-small cell lung cancer. In randomized clinical trials, the addition of bevacizumab to standard therapy has demonstrated significant benefits in progression-free and/or overall survival (*Table 1*).

This review will delineate the safety profile of bevacizumab for oncologists considering using this agent who may not be familiar with side effects of VEGF-targeted therapy, and provide practical guidance on using bevacizumab appropriately in clinical practice and managing patients experiencing typical side effects.

Methods

Eight oncologists with extensive experience in treating patients with bevacizumab in the pivotal trials and a cardiologist with experience of treating a broad range of patients with cardiovascular side effects of cancer treatment were invited to analyse data from eight randomized, phase III clinical trials of bevacizumab in patients with metastatic breast cancer (Miller et al, 2007; Miles et al, 2010), metastatic colorectal cancer (Hurwitz et al, 2004; Giantonio et al, 2007; Saltz et al, 2008), metastatic renal cell carcinoma (Escudier et al, 2007) and metastatic non-small cell lung cancer (Sandler et al, 2006a; Reck et al, 2009). Data from more than 8000 patients treated in large observational studies in metastatic colorectal cancer (BRiTE and BEAT) (Kozloff et al, 2009; Van Cutsem et al, 2009), metastatic breast cancer (ATHENA; Smith et al, 2010) and metastatic non-small cell lung cancer (SAiL; Crinò et al, 2010) were also considered. The data available at the time of the consensus meeting are supplemented in this article with more recently published data if available. However, trials that had not been reported at the time of the consensus meeting (RIBBON-1 and RIBBON-2 in metastatic breast cancer, CALGB 90206 in metastatic renal cell carcinoma) are not included in this article.

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Findings

Most adverse events associated with bevacizumab are mild or moderate (National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 1/2; National Cancer Institute, 2006).

Hypertension

Hypertension is a well-recognized but manageable side effect of anti-VEGF therapies, including bevacizumab.

Mechanism

There are several hypotheses for the cause of hypertension. VEGF upregulates endothelial nitric oxide synthase, causing increased nitric oxide production and vasodilation (Hood et al, 1998). Blockade of VEGF may decrease vascular nitric oxide concentrations, leading to vasoconstriction and hypertension. Long-term endothelial nitric oxide synthase inhibition also increases expression of plasminogen activator inhibitor-1, a key regulator of fibrinolysis and thrombolysis (Katoh et al, 2000), potentially exacerbating existing hypertension (Dincer and Altundag, 2006). In patients with metastatic renal cell carcinoma, additional mechanisms for hypertension include hyper-reninaemia, vasculitis, polycythaemia, hypercalcaemia and renal arteriovenous fistulae (Thomas et al, 1998).

Definitions

In the pivotal bevacizumab trials, hypertension was classified using either version 2 or version 3 of the NCI-

CTCAE (*Table 2*). The definition of hypertension adopted in the UK by the National Institute for Health and Clinical Excellence (NICE) is a persistently raised blood pressure above 140/90 mmHg (National Institute for Clinical Excellence, 2006). Current NICE guidance recommends pharmacological treatment of blood pressure persistently >160/90 mmHg or >140/90 mmHg in patients with known cardiovascular disease, evidence of end-organ damage or a 10-year risk of cardiovascular disease of at least 20%. Accelerated or malignant phase hypertension occurs when there is acute end-organ damage caused by very high blood pressure. This may be asymptomatic or associated with visual disturbances, headache or other vascular complication. Retinal signs including bilateral haemorrhages, exudates or cotton-wool spots are characteristic. Malignant hypertension is a medical emergency and requires hospital admission for assessment, investigation and urgent antihypertensive therapy. This would be included in the definition of NCI-CTCAE grade 4 hypertension.

Table 1. Pivotal phase III bevacizumab clinical trials

			Progression-free survival				
Disease	Trial	Treatment	Hazard ratio	*P* value	Median (months)	Response rate (%)	Median overall survival (months)
Metastatic breast cancer	E2100: first line (Miller et al, 2007)	Bevacizumab 10 mg/kg q2w + paclitaxel (*n*=347)	0.60	<0.001	11.8	37	26.7
		Paclitaxel (*n*=326)			5.9	21	25.2
	AVADO: first line (Miles et al, 2010)	Bevacizumab 7.5 mg/kg q3w + docetaxel (*n*=248)	0.80	0.045†	9.0	55	30.8
		Bevacizumab 15 mg/kg q3w + docetaxel (*n*=247)	0.67	<0.001†	10.0	64	30.2
		Placebo + docetaxel (*n*=241)			8.1	46	31.9
Metastatic colorectal cancer	AVF2107g: first line (Hurwitz et al, 2004)	Bevacizumab 5 mg/kg q2w + IFL (*n*=402)	0.54	<0.001	10.6	45	20.3*‡
		Placebo + IFL (*n*=411)			6.2	35	15.6
	E3200: pretreated (Giantonio et al, 2007)	Bevacizumab 10 mg/kg q2w + FOLFOX4 (*n*=286)	0.61	<0.0001	7.3	23	12.9*§
		Bevacizumab 10 mg/kg q2w (*n*=243)	NA	NA	2.7	3	10.2
		FOLFOX4 (*n*=291)			4.7	9	10.8
	NO16966: first line (Saltz et al, 2008)	Bevacizumab 7.5 mg/kg q3w + XELOX/FOLFOX4 (*n*=699)	0.83	0.0023	9.4	47	21.3
		Placebo + XELOX/FOLFOX4 (*n*=701)			8.0	49	19.9
Metastatic renal cell cancer	AVOREN: first line (Escudier et al, 2007, 2010)	Bevacizumab 10 mg/kg q2w + interferon-α (*n*=327)	0.63	0.0001	10.2	31	23.3
		Placebo + interferon-α (*n*=322)			5.4	13	21.3
Metastatic non-small cell lung cancer	E4599: first line (Sandler et al, 2006a)	Bevacizumab 15 mg/kg q3w + paclitaxel + carboplatin (*n*=417)	0.66	<0.001	6.2	35	12.3*¶
		Paclitaxel + carboplatin (*n*=433)			4.5	15	10.3
	AVAiL: first line (Reck et al, 2009, 2010)	Bevacizumab 7.5 mg/kg q3w + cisplatin + gemcitabine (*n*=345)	0.75	0.003	6.7	34	13.6
		Bevacizumab 15 mg/kg q3w + cisplatin + gemcitabine (*n*=351)	0.82	0.03	6.5	30	13.4
		Placebo + cisplatin + gemcitabine (*n*=347)			6.1	20	13.1

FOLFOX4 = oxaliplatin + fluorouracil + leucovorin; IFL = irinotecan + fluorouracil + leucovorin; XELOX = oxaliplatin + capecitabine; NA = data not available. *Significant overall survival benefit with bevacizumab; † exploratory *P* value; ‡ hazard ratio 0.66 (*P*<0.001); § hazard ratio 0.75 (*P*=0.0011); ¶ hazard ratio 0.79 (*P*=0.003). q2w = every 2 weeks, q3w= every 3 weeks

Table 2. Differences in hypertension grading between versions of National Cancer Institute Common Terminology Criteria for Adverse Events

	Version 2* (National Cancer Institute, 1998)	Version 3† (National Cancer Institute, 2006)
Grade 1	Asymptomatic, transient (<24 hour) blood pressure increase of >20 mmHg (diastolic) or to >150/100 mmHg if previously normal. Intervention is not required for grade 1 hypertension	
Grade 2	Recurrent, persistent (≥24 hour) or symptomatic blood pressure increase of >20 mmHg (diastolic) or to >150/100 mmHg if previously normal. Antihypertensive treatment not required	Recurrent, persistent (≥24 hour) or symptomatic blood pressure increase of >20 mmHg (diastolic) or to >150/100 mmHg if previously normal. A single antihypertensive agent may be indicated
Grade 3	Requiring antihypertensive therapy or more intensive therapy	Requires more than one agent or more intensive therapy
Grade 4	Hypertension with life-threatening consequences (e.g. hypertensive crisis)	

*Used in E2100, AVF2107g, E3200 and E4599 trials. † Used in AVADO, NO16966, AVOREN and AVAiL trials

Incidence

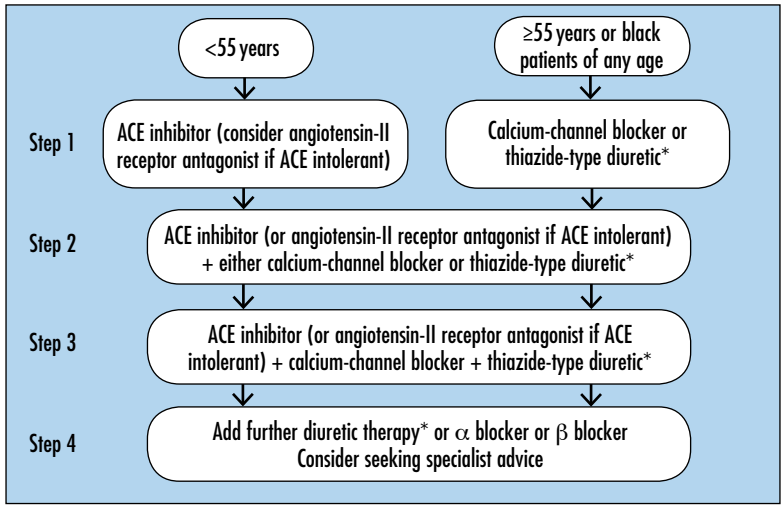
Hypertension reporting is not consistent in oncology clinical trials. Some report only NCI-CTCAE hypertension grades, some report absolute blood pressure and some report the initiation of antihypertensive therapy. In addition, some studies have an inherent reporting bias: in one trial (E2100), an intergroup-sponsored study, adverse event reporting was mandatory only in the bevacizumab-containing arm (Miller et al, 2007).

In the pivotal phase III clinical trials, hypertension occurred more frequently in bevacizumab-containing treatment groups than in the control arms (*Table 3*). However, the majority of cases were grade 1–3, even among patients who had undergone nephrectomy for metastatic renal cell carcinoma, and consequently were manageable with standard antihypertensive medication. The apparent variability in the incidence of hypertension may be caused by differences in reporting and distinguishing grades 2 and 3. Study population differences may also contribute, for example predisposing factors for development of hypertension (e.g. VEGF single nucleotide polymorphisms) (Schneider et al, 2008).

Recommendations before starting bevacizumab

Blood pressure should be monitored before and during bevacizumab therapy. Pre-existing hypertension must be controlled before starting treatment. As soon as a diagnosis of hypertension is made, antihypertensive treatment should be initiated. Blood pressure should be reviewed after a few days and further medication given if necessary. Satisfactory control of blood pressure can be achieved for most patients within 1 week, which corresponds to the typical delay in starting chemotherapy after diagnosis of cancer. If previously undiagnosed hypertension is detected, antihypertensive therapy should be given to achieve a target blood pressure of <140/90 mmHg before starting bevacizumab. Hypertension should always be managed in partnership with the patient's GP, who should be informed of the reason for initiating treatment and the target blood pressure. Treatment can then be continued, monitored and titrated in primary care. Drug treatment should follow NICE guidance (*Figure 1*).

Figure 1. National Institute for Clinical Excellence (2006) guidelines for antihypertensive therapy in patients with newly diagnosed hypertension. ACE = angiotensin-converting enzyme. *Diuretics not advised in patients receiving cisplatin-based chemotherapy (Roche, 2010).



Hypertension during bevacizumab treatment

Transient blood pressure elevation should be excluded by remeasurement after 30 minutes. *Table 4* summarizes the recommendations according to blood pressure elevation.

Antihypertensive treatment should follow NICE (2006) guidelines (*Figure 1*) for pre-existing hypertension. If a patient develops hypertension that cannot be controlled to consistently <180/110 mmHg, bevacizumab should be withheld and the patient should be referred to a hypertension specialist. If a patient develops grade 4 hypertension (malignant phase hypertension or evidence of encephalopathy, angina, heart failure or altered consciousness), the patient should be discussed with an on-call medical team and admitted to high-dependency care, with oral or intravenous blood pressure management. Bevacizumab should be withheld permanently.

In cases of uncomplicated severe hypertension (diastolic blood pressure >120 mmHg), the blood pressure can be reduced gradually with oral agents (not sublingual or capsular nifedipine) without the need for immediate blood pressure reduction with parenteral drugs. In cases of hypertensive crisis, where elevated blood pressure causes an acute clinical problem such as hypertensive encephalopathy, management is likely to involve parenteral agents, such as nitroglycerin, labetalol, esmolol, nicardipine, nitroprusside, hydralazine or phentolamine, depending on the clinical scenario to reduce mean arterial blood pressure by no more than 25% over the first hour, then to 160/100–110 mmHg over the next 2–6 hours (National Heart, Lung, and Blood Institute, 2004).

When bevacizumab treatment is stopped, the need for ongoing antihypertensive medication should be reassessed.

Proteinuria

Mechanism and definitions

VEGF is required for growth and proliferation of glomerular and peritubular endothelial cells (Eremina et al, 2003; Schrijvers et al, 2004). Treatment with a VEGF inhibitor may disrupt this network, leading to glomerular dysfunction and proteinuria. Proteinuria was classified according to NCI-CTCAE in bevacizumab pivotal trials (National Cancer Institute, 2006). Grade 1 proteinuria is dipstick 1+ or urinary protein 0.15–1.0 g/24 hours, grade 2 is dipstick 2+ or 3+ or urinary protein >1.0–3.5 g/24 hours, grade 3 is dipstick 4+ or urinary protein >3.5 g/24 hours, and grade 4 proteinuria is nephrotic syndrome.

Incidence

Grade 3 or 4 proteinuria was reported in <1% of patients treated in the metastatic colorectal cancer trials, <2% of

Table 3. Most common toxicities associated with bevacizumab: incidence of grade 3 and 4 events in pivotal phase III trials

Disease	Treatment and reference	Grade	Hypertension		Proteinuria		Haemorrhage			ATE		VTE		Wound healing complications		Gastrointestinal perforation			Congestive heart failure		
			3	4	3	4	3	4	5	3	4	3	4	3	4	3	4	5	3	4	5
Metastatic breast cancer	E2100: first line (Miles, 2008)	Bevacizumab 10 mg/kg q2w + paclitaxel (*n*=363)	15.4	0.6	1.9	1.1	1.7	0.6	0	1.1	1.9	--3.0--		--1.1--		0	0	0.6	--2.2--		
		Paclitaxel (*n*=348)	1.4	0	0	0	0.3	0	0	0	0	--4.3--		--0--		0	0	0	--0.3--		
	AVADO: first line (Miles et al, 2010)	Bevacizumab 7.5 mg/kg q3w + docetaxel (*n*=252)	--0.8--		--0.8--		--1.2--		0	--0--		--1.6--		--0.4--		--0.4--		0	--1.2--		0
		Bevacizumab 15 mg/kg q3w + docetaxel (*n*=247)	--4.5--		--2.0--		0.8		0.8	0.8		1.2		--0.4--		--0--		0.4	--0--		0
		Placebo + docetaxel (*n*=231)	--1.3--		--0--		0.9		0	0*		3.0*		--0.9--		--0.9--		0	--0--		0
Metastatic colorectal cancer	AVF2107g: first line (Hurwitz et al, 2004)	Bevacizumab 5 mg/kg q2w + IFL (*n*=393)	11.0	0	0.8	0	--3.1--		NR	NR	NR	NR	NR	NR (1.3 all grades)		--1.2--		0.3	NR		
		Placebo + IFL (*n*=411)	2.3	0	0.8	0	--2.5--		NR	NR	NR	NR	NR	NR (0.3 all grades)		--0--		0	--0--		0.3
	E3200: pretreated (Giantonio et al, 2007)	Bevacizumab 10 mg/kg q2w + FOLFOX4 (*n*=287)	5.2	1.0	0.7	0	3.1	0.3	0.3	3.1¶		0.3**		NR		1.0 (all grades)†			NR		
		Bevacizumab 10 mg/kg q2w (*n*=234)	1.4	0.4	0	0	2.1	0	0.4	0¶		0.4**		NR		1.3 (all grades)†			NR		
		FOLFOX4 (*n*=285)	7.3	0	0	0	0.4	0	0	1.1¶		1.4**		NR		0 (all grades)†			NR		
	NO16966: first line (Saltz et al, 2008)	Bevacizumab 7.5 mg/kg q3w + XELOX/FOLFOX4 (*n*=694)	--3.7--		--0.6--		--1.9--			--1.7‡--		--7.8--		--0.1--		--0.4--		0.1	NR		
		Placebo + XELOX/FOLFOX4 (*n*=675)	--1.2--		--0--		--1.2--			--1.0‡--		--4.9--		--0.3--		--0.1--		0.1	NR		
Metastatic renal cell cancer	AVOREN: first line (Escudier et al, 2007)	Bevacizumab 10 mg/kg q2w + interferon-α (*n*=337)	--3.3--		--6.5--		--2.7--		0.6	--1.2--		--1.8--		--0.6--		0	0.9	0.3	--0.3--		
		Placebo + interferon-α (*n*=304)	--0.7--		--0--		--0.3--			--0.3--		--0.7--		--0--		0	0	0	0	0	0
Metastatic non-small cell lung cancer	E4599: first line (Sandler et al, 2006a)	Bevacizumab 15 mg/kg q3w + paclitaxel + carboplatin (*n*=427)	6.8	0.2	2.6	0.5	--4.4--			NR		NR		NR			NR			NR	
		Paclitaxel + carboplatin (*n*=440)	0.5	0.2	0	0	--0.7--			NR		NR					NR				
	AVAiL: first line (Reck et al, 2009)	Bevacizumab 7.5 mg/kg q3w + cisplatin + gemcitabine (*n*=345)	--6.4--		--0.3--		--4.2--			--2.4§--		--7.3--		NR		0	0	0		NR	
		Bevacizumab 15 mg/kg q3w + cisplatin + gemcitabine (*n*=351)	--8.5--		--1.2--		--4.3--			--3.0§--		--7.0--					--0.3--			NR	
		Placebo + cisplatin + gemcitabine (*n*=347)	--1.5--		--0--		--1.8--			--4.5§--		--6.4--					--0.6--			NR	

ATE = arterial thromboembolic events; FOLFOX4 = oxaliplatin + fluorouracil + leucovorin; IFL = irinotecan + fluorouracil + leucovorin; NR = not reported; q2w = every 2 weeks; q3w = every 3 weeks; VTE = venous thromboembolic events; XELOX = oxaliplatin + capecitabine. * Plus one grade 5 event; † Fatal in one patient. ‡ Includes ischaemic cardiac events; § Ischaemic events including ATE; ¶ Grade 3 arterial and venous thromboembolic events combined; **Grade 4 arterial and venous thromboembolic events combined.

Table 4. Managing patients developing hypertension during bevacizumab therapy

	Blood pressure during bevacizumab therapy			
	<160/100 mmHg	160/100–180/110 mmHg	>180/110 mmHg	Malignant phase hypertension*
Bevacizumab administration	Continue	Continue unless increased cardiovascular risk	Suspend until blood pressure <160/100 mmHg	Discontinue permanently
Hypertension referral	Not required	Not required unless blood pressure remains >160/100 mmHg despite step 3 of NICE guidance or multiple drug intolerance or contraindications	Refer for specialist management	Emergency referral – discuss admission to high-dependency care with on-call medical team
Antihypertensive treatment	Not required	Start or increase in accordance with NICE guidance	Start or increase in accordance with NICE guidance	Parenteral treatment with invasive monitoring

*signs of end-organ damage, encephalopathy, angina, heart failure or altered consciousness. From National Institute for Clinical Excellence (NICE) (2006)

patients treated in the metastatic breast cancer trials and in 6.5% of patients treated for metastatic renal cell carcinoma (*Table 3*). In large observational studies of bevacizumab and chemotherapy in metastatic colorectal cancer, metastatic breast cancer and metastatic non-small cell lung cancer, grade ≥3 proteinuria occurred in 1.1–3.0% of patients (Van Cutsem et al, 2009; Crinò et al, 2010; Smith et al, 2010). A possible dose-relationship between bevacizumab and grade 1 proteinuria has been seen in clinical trials (Roche, 2010). Bevacizumab-induced proteinuria has not been associated with renal dysfunction (Roche, 2010) and is reversible, although any long-term effects are unknown.

Guidelines for evaluation and treatment

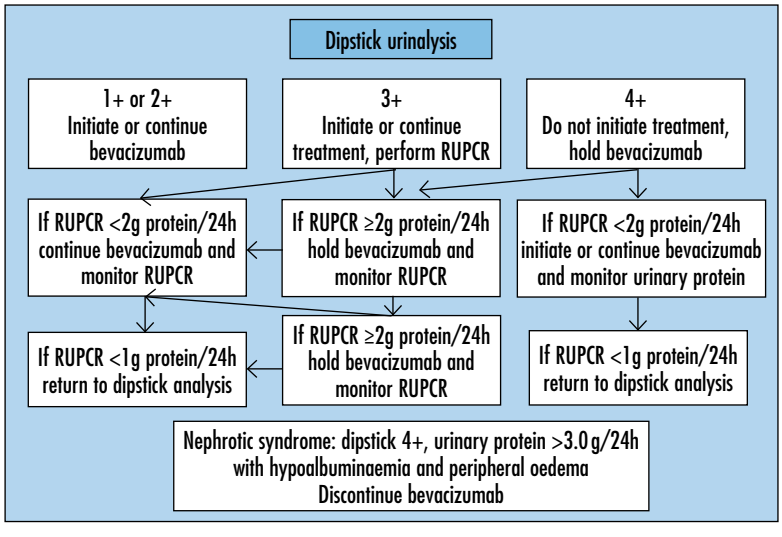
Proteinuria should be assessed in the context of the underlying disease. *Figure 2* summarizes recommendations for assessing and managing proteinuria in patients receiving bevacizumab.

Haemorrhage

Mechanism, grading and incidence

VEGF is involved in regeneration of the vascular endothelium and maintaining the integrity of the vascular lining (Kilickap et al, 2003). Disruption of these processes by VEGF inhibition may cause bleeding in epithelial tissues that depend on continuous VEGF signalling for normal functioning and maintenance of structural integrity.

Figure 2. Algorithm for proteinuria testing and procedure. RUPCR = random urine protein:creatinine ratio.



Haemorrhage was graded according to NCI-CTCAE in the pivotal clinical trials of bevacizumab. Grade 1 haemorrhage is mild and no intervention is indicated, grade 2 requires symptomatic medical intervention, grade 3 requires transfusion and grade 4 has life-threatening consequences, necessitating urgent major intervention. Bevacizumab-related bleeding is usually minor and requires minimal or no medical intervention. The most common types of haemorrhage with bevacizumab are minor mucocutaneous bleeds. For example, a patient may experience bleeding gums, blood-stained mucus after blowing the nose or epistaxis requiring only basic first aid. Bleeding from haemorrhoids may occur. Menstruating women may experience longer and heavier bleeding during menses. Women receiving bevacizumab with chemotherapy may experience chemotherapy-induced amenorrhoea or menstrual cycle suppression. Grade 3 or 4 bleeds with bevacizumab occurred in 1.2–4.4% of patients in the pivotal trials (*Table 3*). The incidence in four large observational studies in metastatic colorectal cancer, metastatic breast cancer and non-small cell lung cancer fell within this range (1.4–3.6%) (Kozloff et al, 2009; Van Cutsem et al, 2009; Crinò et al, 2010; Smith et al, 2010).

Guidelines for evaluation and treatment

If patients experience grade 3 or 4 bleeding, standard measures should be taken to control bleeding and normalize blood volume. Bevacizumab should be discontinued and reinstated only when the cause of the bleed has been identified and managed. Otherwise bevacizumab should be permanently discontinued. In patients with recent peptic ulceration, bevacizumab should be discontinued until endoscopic confirmation of healing.

Patients receiving full-dose anticoagulants for thromboembolism were excluded from some early bevacizumab trials but not more recent ones. Data from AVAiL (Reck et al, 2009), AVADO (Wardley et al, 2009) and BRiTE (Kozloff et al, 2009) suggest that bevacizumab may be given in these patients. Nevertheless, the usual precautions should be observed in this patient population and in those

with congenital bleeding diathesis and acquired coagulopathy. Patients receiving low-dose aspirin (Hambleton et al, 2005) or stabilized warfarin therapy (Hambleton et al, 2004) do not appear to be at increased risk of bleeding during bevacizumab therapy. No data are available for concurrent use of bevacizumab and clopidogrel.

Tumour-related bleeding

In metastatic breast cancer, metastatic colorectal cancer and metastatic renal cell carcinoma the risk of tumour-associated bleeding during bevacizumab therapy appears to be low and therefore special monitoring is not warranted. Risk may be increased in patients receiving bevacizumab for metastatic and stage IIIb non-small cell lung cancer. Serious haemoptysis was reported in 9% of non-small cell lung cancer patients treated with bevacizumab plus chemotherapy in a phase II study, leading to death in 6% (Johnson et al, 2004). These patients had squamous cell histology and/or tumours located in the centre of the chest close to major blood vessels. In the two phase III trials in metastatic non-small cell lung cancer, patients with tumours invading major vessels were excluded. Patients had to have non-squamous predominant tumours with minimal or no baseline haemoptysis. These precautions resulted in a substantially lower incidence of grade ≥3 haemoptysis: 1.9% in the E4599 trial (Sandler et al, 2006a) and ≤1.5% in the AVAiL trial (Reck et al, 2009).

Based on these observations and an analysis of phase II and III trials (Sandler et al, 2006b), bevacizumab should not be given to metastatic non-small cell lung cancer patients with predominantly squamous histology, recent pulmonary haemorrhage or haemoptysis (>2.5 ml of blood), tumours invading major vessels, or presence of tumour cavitation. Furthermore, if patients experience pulmonary haemorrhage (any grade) or significant haemoptysis, permanent discontinuation of bevacizumab is recommended. Patients with brain metastases were excluded from early bevacizumab clinical trials. However, an analysis of >12 000 patients treated in clinical trials suggested that the risk of CNS haemorrhage in patients with CNS progression was not disproportionately high (Besse et al, 2010). While it is recommended that bevacizumab therapy is stopped if a patient experiences a detectable cerebral bleed, use of bevacizumab in patients with untreated CNS metastases is not contraindicated.

Of note, bevacizumab has shown activity and is under further evaluation for the treatment of glioblastoma (Vredenburgh et al, 2007; Friedman et al, 2009).

Thromboembolism

Grade 3 or 4 arterial thromboembolic events (stroke, transient ischaemic attacks and myocardial infarction) occurred in ≤3% of patients receiving bevacizumab in the pivotal trials. An analysis of five randomized controlled trials (n=1745; metastatic colorectal cancer, metastatic breast cancer, metastatic non-small cell lung cancer) showed an increased risk of arterial thromboembolic events in patients receiving bevacizumab plus chemotherapy *vs* chemotherapy alone (Scappaticci et al, 2007). Patients with a history of arterial thromboembolic events and/or aged ≥65 years are at increased risk of developing an arterial thromboembolic event during bevacizumab therapy (Scappaticci et al, 2007). Bevacizumab should be discontinued if a patient experiences an arterial thromboembolic event during treatment.

The pooled analysis of five trials described above demonstrated no increased risk of venous thromboembolism in patients receiving bevacizumab (Scappaticci et al, 2007). A more recent analysis of individual patient data from more than 6000 patients treated in 10 randomized trials also revealed no increase in risk of venous thromboembolism among patients receiving bevacizumab compared with controls (Cassidy et al, 2010). The risk varied according to tumour type. Bevacizumab should be discontinued if a patient develops a grade 4 pulmonary embolism. Any patient experiencing a grade ≤3 venous thromboembolism should be monitored closely.

Delay in wound healing and wound complications

Bevacizumab may affect wound healing post-surgery (*Table 3*). Patients who had undergone surgery within the preceding 28 days were excluded from pivotal clinical trials of bevacizumab. However, there was no evidence of more severe or frequent wound healing complications among patients undergoing on-study surgery in the AVADO trial with bevacizumab compared with placebo (Cortés et al, 2009). In observational studies, grade 3 or 4 wound healing complications were reported in 0.6% of patients with metastatic breast cancer (Smith et al, 2010) and <0.1% of those with metastatic non-small cell lung cancer (Crinò et al, 2010). There was no apparent excess wound complications when bevacizumab was given for metastatic colorectal cancer 28–60 days after surgery compared with patients receiving chemotherapy alone (Scappaticci et al, 2005).

Data from 521 patients with metastatic colorectal cancer undergoing surgery within 90 days of bevacizumab-containing therapy in the BRiTE study support these findings (Kozloff et al, 2009). The overall rate of wound healing complications was 4.4%, and was lower (2.2%) in those who underwent surgery >8 weeks after the last dose of bevacizumab. The approximate mean elimination half-life of bevacizumab is 18–20 days (Roche, 2010). The risk of wound complications and the timing of surgery should take these factors into account. As shown in *Figure 3* summarizing suggested strategies, bevacizumab is not an absolute contraindication to emergency surgery. If venous access needs to be re-established during bevacizumab therapy, another peripheral central catheter or port should be inserted. When the wound has healed, treatment with bevacizumab may be re-initiated.

Gastrointestinal perforation

The incidence of gastrointestinal perforation varies according to tumour type (*Table 3*). In metastatic non-small cell

lung cancer trials and the placebo-controlled AVADO metastatic breast cancer trial, there was no increase in the incidence of grade 3–5 gastrointestinal perforation in the bevacizumab arms. The 0.3% incidence in ATHENA (Smith et al, 2010) is within the range reported in E2100 and AVADO. In metastatic colorectal cancer, grade 3–5 gastrointestinal perforation occurred in up to 1.5% of patients, including fatal events in 0.3% (Hurwitz et al, 2004; Giantonio et al, 2007; Saltz et al, 2008). The risk of perforation is increased in the presence of acute diverticulitis, intestinal obstruction or abdominal carcinomatosis, and with a colonic or rectal stent. Any enteric fistula is a contraindication for treatment with bevacizumab. Use of bevacizumab in patients with a colonic or rectal stent may not be advisable. Invasive procedures (e.g. gastrointestinal endoscopy), peptic ulcer disease, diverticulosis or chronic aspirin use may also add to the risk.

Patients should report any change in abdominal pain, which should be assessed immediately. If a perforation develops bevacizumab should be discontinued and surgical advice should be sought.

Congestive heart failure or cardiomyopathy

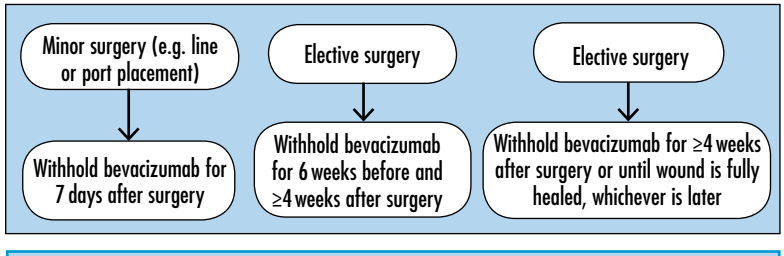
Congestive heart failure is rare in patients treated with bevacizumab. The low incidence and differences in congestive heart failure reporting make accurate estimation of the excess risk difficult, but the incidence of grade 3 or 4 congestive heart failure is consistently <1% (*Table 3*). If congestive heart failure or cardiomyopathy occurs, bevacizumab should be discontinued, angiotensin-converting enzyme inhibitor therapy should be initiated and the patient referred for specialist review. Routine cardiac monitoring is not generally necessary.

Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome is thought to result from changes to the blood–brain barrier, leading to entry of fluid and protein into the extravascular space, resulting in cerebral oedema (Shah-Khan et al, 2007). Symptoms of reversible posterior leukoencephalopathy include nausea, vomiting, seizures, headaches, altered mental status, visual disturbance and cortical blindness (Shah-Khan et al, 2007). Magnetic resonance imaging can be used to exclude CNS metastases and confirm a diagnosis of reversible posterior leukoencephalopathy.

Reversible posterior leukoencephalopathy has been reported with both chemotherapy and targeted agents. Symptoms consistent with reversible posterior leukoencephalopathy have been reported in five patients treated with bevacizumab-containing regimens (Shah-Khan et al, 2007; Levy et al, 2009) but no cases were reported in the randomized trials of bevacizumab. If reversible posterior leukoencephalopathy is suspected, it is recommended to seek specialist neurological opinion, control any hypertension and specific symptoms and discontinue bevacizumab permanently.

Figure 3. Algorithm for surgery in patients receiving bevacizumab.



KEY POINTS

- The safety profile of bevacizumab has been well defined in several large, randomized phase III clinical trials, supporting observational studies and post-marketing surveillance of more than 800 000 patients treated worldwide.
- Most adverse effects of bevacizumab are predictable and manageable.
- Simple algorithms outlined in this article can be used to reduce the risk of adverse effects of bevacizumab and manage any adverse events that occur.

Conclusions

In patients with metastatic breast cancer, metastatic colorectal cancer, metastatic renal cell carcinoma and non-small cell lung cancer, bevacizumab combined with standard therapy significantly improves progression-free survival and, in some tumour types, overall survival. Very recently, results from the GOG218 (Burger et al, 2010) and ICON7 (Peren et al, 2010) trials have demonstrated significantly improved progression-free survival (the primary end point) when bevacizumab is combined with standard front-line therapy in ovarian cancer and continued as single-agent maintenance therapy. The safety profile of bevacizumab has been well defined in more than 800 000 cancer patients treated worldwide and most adverse events are predictable and manageable. **BJHM**

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