

Management Guidelines for Bevacizumab-Related Side Effects in Patients with Colorectal Cancer

Bevacizumab (AVASTIN®) is a humanized anti-VEGF monoclonal antibody that has meaningful clinical activity in patients with metastatic colorectal cancer. It significantly improves both the progression-free and overall survival of patients when used with standard chemotherapy. While bevacizumab does not increase the incidence of chemotherapy-related toxicities and is generally well tolerated in combination with chemotherapy, there are some adverse side effects for which monitoring is required. In this document, the side effects noted in clinical trials of bevacizumab are reviewed and guidelines for their monitoring and management provided.

1. Adverse events of bevacizumab in combination with chemotherapy

Bevacizumab is approved for first-line treatment of metastatic colorectal patients in combination with 5-fluorouracil (FU)-based chemotherapy. This includes FU-folinic acid (FUFA) or FU-folinic acid-irinotecan chemotherapy. Bevacizumab also significantly extends the progression-free and overall patient survival when given as second-line treatment with FU-folinic acid-oxaliplatin (FOLFOX). Bevacizumab does not increase the incidence of chemotherapy-related toxicities, such as neutropenia or diarrhea (Table 1) (1-3). In addition, the 60-day all-cause mortality for bevacizumab-treated patients is similar to that for chemotherapy alone. There is no evidence of cumulative or late toxicities (4,5).

Table 1. Incidence of chemotherapy-related toxicities in patients treated chemotherapy with or without bevacizumab

Event (%)	FUFA n=104	Bevacizumab + FUFA n=100	IFL n=397	Bevacizumab + IFL n=393
Grade 3/4 diarrhea	40	39	25	32
Grade 3/4 neutropenia	7	5	31	37
60-day all-cause mortality	14	5	5	3

2. Adverse events due to bevacizumab

A number of adverse events due to bevacizumab have been observed in patients who were treated with bevacizumab in combination with chemotherapy for metastatic colorectal cancer as well as non-small cell lung cancer, breast cancer and prostate cancer. The side effects of bevacizumab include:

- Hypertension
- Proteinuria
- Bleeding
- Arterial and venous thromboembolism
- Delay in wound healing or wound complications
- GI perforation
- Reversible posterior leukoencephalopathy syndrome

Hypertension

Hypertension is a common side effect of bevacizumab therapy. The cause is not entirely clear, but it may be due to decreased production of the vasodilator nitric oxide (NO) by blockade of the VEGF receptors (6). Reduced NO production also leads to reduced renal sodium excretion which may contribute to hypertension (7).

Table 2. Grading scale for hypertension used in clinical trials (CTCAE v2)

1	asymptomatic, transient (<24 hours) increase by >20 mmHG (diastolic) or to >150/100 if previously normal
2	recurrent or persistent or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously normal; monotherapy may be indicated
3	requiring more than one hypertensive or more intensive therapy than previously
4	life-threatening consequence, such as hypertensive crisis

The incidence of hypertension with bevacizumab is 22-32%, but Grade 3 hypertension occurs in 11-16% of patients, and Grade 4 hypertension is rare (1% of patients) (1-3). Hypertension can occur any time after the start of bevacizumab therapy and the blood pressure should, therefore, be checked before each cycle of treatment. An acute rise in blood pressure may occur during bevacizumab infusion. If this occurs, bevacizumab infusion should be stopped and resumed at a slower rate if the blood pressure returns to the pretreatment range.

Treatment of Hypertension

A thiazide diuretic is the first line of treatment, with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) being added as second-line treatment. Alternatively, if there is concomitant renal dysfunction or proteinuria, an ACE inhibitor or ARB (if ACE inhibitor is not tolerated) may be started first with diuretics as additive therapy.

The International Society of Hypertension (ISH) classification is a useful guide to assess the need to start or change antihypertensive therapy.

Category	ISH Classification of Hypertension	
	Systolic	Diastolic
Optimal	<120	<80
Normal	<130	<85
High normal	130-139	85-89
Hypertension		
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	≥180	≥110

Eligibility

Blood pressure <160/100 and on stable antihypertensive medications

Monitoring and recommendations

1. Acute hypertension during bevacizumab infusion

During the first three cycles of bevacizumab, blood pressure should be checked before treatment, midway during treatment, and at the end of treatment.

- If acute hypertension (increase by >20mmHg diastolic or >160/100 if previously within normal limits) occurs during bevacizumab infusion, stop bevacizumab and resume at a slower rate if blood pressure returns to the pretreatment range within one hour.*
- If blood pressure does not return to baseline within one hour, bevacizumab should be held. Subsequent infusion of bevacizumab should be given at a slower rate (3 hours).*
- Acute hypertension that is symptomatic (e.g. onset of headaches or change in level of consciousness) or grade 3 hypertension (≥180/110) that does not improve after one hour of stopping bevacizumab is an urgent situation requiring treatment. If the pulse rate is >65, labetalol may be given; if the pulse rate is <65, hydralazine may be used. Consultation with a cardiologist or emergency room physician is recommended for advice about therapy and monitoring.*

2. Hypertension during course of treatment with bevacizumab

Patients treated with bevacizumab should have their blood pressure monitored every 2 to 3 weeks while on therapy.

- *Grade 1: Continue bevacizumab. No intervention required. Continue to monitor blood pressure.*
- *Grade 2: Stop bevacizumab temporarily and start oral antihypertensive medication. If hypertension is controlled with blood pressure returning to pretreatment level or <160/100, restart bevacizumab and continue to monitor blood pressure.*
- *Grade 3: Bevacizumab therapy should be interrupted until adequate control is achieved by antihypertensive medications. If hypertension is uncontrolled after one month, bevacizumab therapy should be discontinued.*
- *Hypertensive crisis: Discontinue bevacizumab.*

Proteinuria

Table 3. Grading scale for proteinuria

Grade 1	1+ or 0.15-1.0 g/24 hours
Grade 2	2+ to 3+ or >1.0 – 3.5 g/24 hours
Grade 3	4+ or >3.5 g/24 hours
Grade 4	nephrotic syndrome

Proteinuria occurs in 27-38% of patients receiving bevacizumab. It is usually asymptomatic (Grade 1 or 2) and Grade 3 or 4 proteinuria is rare (1%) (1-3). Proteinuria is not associated with renal dysfunction, and it improves after bevacizumab is stopped. The mechanism of proteinuria is not fully understood, but is likely due to a glomerular effect, such as membrano-proliferative glomerulonephritis. Glomerular endothelial repair may require VEGF and anti-VEGF therapy, thus, interferes with glomerular endothelial integrity (8). In addition, erythropoietin stimulates VEGF release in the glomerulus and the low levels of erythropoietin in cancer patients may aggravate the condition (9). There appears to be an association between the occurrence of proteinuria and hypertension, either pre-existing or induced by bevacizumab.

Eligibility

- *Dipstick urinalysis shows no proteinuria or 1+ proteinuria*
- *If dipstick urinalysis shows \geq 2+ proteinuria, 24-hour urine for protein must be \leq 2g*

Monitoring and recommendations

Dipstick urinalysis should be done before each cycle of bevacizumab.

Grade 1: Continue bevacizumab. No additional investigation; continue to monitor.

Grade 2: Give bevacizumab and collect 24-hour urine within 3 days before next cycle

- *24-hour proteinuria \leq 2g: Give bevacizumab. Continue to follow by 24-hour urinary protein before each cycle. If urinary protein falls to <1 g, resume monitoring by dipstick method.*
- *24-hour proteinuria >2g: Hold bevacizumab and repeat 24-hour urine collection for proteinuria before the next cycle.*
 - *Repeat 24-hour proteinuria <2g: Give bevacizumab and continue to check 24-hour protein before each cycle. If protein decreases to <1g, resume monitoring by dipstick urinalysis*
 - *Repeat 24-hour urine >2g: Hold bevacizumab and continue to check before each cycle of treatment. Give bevacizumab if protein decreases to <2g. If not <2 g after 3 months, discontinue bevacizumab*

Grade 3: Hold and check 24-hour urinary protein. Restart bevacizumab if 24-hour urinary protein decreases to <2 g. If not <2g after 3 months, discontinue bevacizumab.

Grade 4: Discontinue bevacizumab.

Bleeding

Table 4. Grading scale for bleeding

1	Mild; intervention not indicated
2	symptomatic and medical intervention indicated
3	transfusion, interventional radiology, endoscopic or operative intervention indicated (i.e. hemostasis of bleeding site)
4	life-threatening consequences; major urgent intervention indicated

Bleeding from the mucocutaneous membranes is common with bevacizumab treatment and occurs in 20-40% of patients. This is mainly epistaxis which responds to usual first-aid techniques with cessation of bleeding within 5 minutes. Gingival bleeding may also occur. Menstruating women may notice longer and heavier uterine bleeding during the menses. Tumor-associated hemorrhage can also occur.

The incidence of Grade 3/4 bleeding in patients receiving bevacizumab 5mg/kg every 2 weeks is 3.1-5.1%, and the incidence appears higher when the dose of bevacizumab is 10mg/kg every 2 weeks (9.4%). This compares with an incidence of 2.5-2.9% in those patients receiving chemotherapy alone (1-3).

The incidence of tumor-related hemorrhage in patients with colorectal cancer receiving bevacizumab is 3-5% and is comparable with that for patients on chemotherapy alone (17). It is noteworthy that in a Phase II study of patients with non-small cell lung cancer, a relatively high rate of hemorrhage was observed (9%) with a mortality rate of 6%. Squamous cell histology and central location of the tumor next to major blood vessels appear to predispose to this complication (10).

The risk of intracranial hemorrhage in patients with brain metastases is not known. Also, patients with inherited or acquired coagulopathy should be treated with caution. In addition, patients on full-dose anticoagulant therapy for thrombosis prior to starting bevacizumab should be treated with caution. However, anticoagulation can be safely given in patients who develop venous thrombosis while on bevacizumab therapy (11).

Recommendations

- 1. Patients receiving bevacizumab should be monitored for bleeding. Most episodes of bleeding are minor, usually nosebleeds or other mucocutaneous bleeding, and appropriate measures should be employed.*
- 2. When red cell transfusion or major intervention is required (Grade 3 or 4), bevacizumab should be discontinued.*
- 3. Do not use in patients with untreated brain metastases.*
- 4. Use with caution in patients with inherited or acquired coagulopathy.*

Thromboembolism

A. Venous thromboembolism

Table 5. Grading scale for venous thromboembolism

1	NA
2	deep vein thrombosis (DVT) or cardiac thrombosis; intervention (e.g. anticoagulation, lysis, filter, invasive procedure) not indicated
3	DVT or cardiac thrombosis; intervention (anticoagulation, lysis, filter, invasive procedure) indicated
4	embolic event including pulmonary embolism or life-threatening thrombosis

There is not an increase in the incidence of venous thromboembolism in patients receiving bevacizumab therapy (1-3). However, if grade 3 venous thrombo-embolic event or incidentally discovered pulmonary embolus occurs, bevacizumab should be held for two weeks while anticoagulant treatment is initiated. Bevacizumab may be restarted if the patient is on a stable dose of anticoagulants. For pulmonary embolism (grade 4 venous embolic event), bevacizumab should be stopped and anticoagulant therapy started. Bevacizumab may be resumed if the patient is stable and adequate anticoagulation achieved. If any life-threatening thromboembolism occurs, bevacizumab should be discontinued.

B. Arterial thromboembolism

An increase in incidence of arterial thromboembolism is observed in patients treated with bevacizumab compared with those receiving chemotherapy alone (4.5% vs. 2%). The mortality rate associated with this is 0.8% and 0.4%, respectively (Table 6). The arterial thromboembolic events include cerebrovascular accident, myocardial infarction, unstable angina, transient ischemic attack, claudication, subarachnoid hemorrhage and other arterial embolic events (2,3).

Table 6. Incidence of arterial thromboembolism in cancer patients receiving bevacizumab therapy (includes colorectal, breast, and non-small cell lung cancer patients)

	Chemotherapy n = 741	Chemotherapy with Bevacizumab n = 1,004
Arterial thromboembolism	15 (2%)	45 (4.5%)
Mortality	3 (0.4%)	8 (0.8%)

Retrospective review of clinical trials data indicate that patients over 65 years of age and those with a previous history of a arterial thromboembolic event are an increased risk for arterial thromboembolic event while on bevacizumab therapy. It is important to note that in the registration study (3), a subgroup analysis of patients over 65 years showed a significant benefit from bevacizumab therapy and it should, therefore, be considered in this group, if appropriate. Of relevance, in an analysis of patients in three randomized clinical trials of bevacizumab, use of low dose aspirin (<325 mg/day) was not associated with increased incidence of bleeding (12). Prophylactic aspirin may be considered for those at high risk of thromboembolism provided there are no contra-indications to its usage.

Recommendations

A. Venous thromboembolism

- 1. Bevacizumab should be held for two weeks in patients with Grade 3 venous thromboembolic events or incidentally discovered pulmonary embolus. Bevacizumab may be resumed after initiation of therapeutic-dose anticoagulant therapy provided the patient is stable and no hemorrhagic complication is present.*
- 2. In the event of a pulmonary embolus, bevacizumab should be stopped and anticoagulant therapy initiated. If the patient is stable and adequate anticoagulation is achieved, bevacizumab may be restarted.*
- 3. Bevacizumab should be discontinued if any life-threatening venous thromboembolic event occurs.*

B. Arterial thromboembolism

- 1. Caution should be taken when starting bevacizumab in patients with a previous history of arterial thromboembolic events or those over 65 years of age.*
- 2. Patients with a recent arterial thromboembolic event (myocardial infarction, TIA, cerebrovascular accident or other event) should not be treated with bevacizumab for at least six months, and bevacizumab should be started only if they are stable and asymptomatic. However, chemotherapy can be initiated before this.*
- 3. Aspirin (<325 mg/day) could be considered for suitable patients at high risk of arterial thromboembolic events.*

4. Patients who develop any arterial thromboembolic event during bevacizumab therapy should be taken off treatment.

5. Patients who develop arterial thromboembolic events can be treated safely with full-dose anticoagulant therapy, such as warfarin, and there does not appear to be an increased risk of bleeding as a result of anticoagulant therapy.

Delay in Surgical Wound Healing and Wound Complications

Bevacizumab therapy can delay wound healing after surgery. Patients who had surgery 28-60 days before starting bevacizumab do not have an increased risk of delayed wound healing or bleeding compared with those who had chemotherapy alone (Tables 7 and 8). In contrast, patients who undergo surgery while on bevacizumab therapy have an increased risk of wound complications (average 13%) compared with those on chemotherapy alone (0%) (13). The wound complications include anastomatic wound dehiscence, ecchymosis and bleeding (3, 13). When elective surgery is planned, waiting 6-8 weeks after the last dose of bevacizumab is advised (14). In such cases, chemotherapy without bevacizumab may be continued until 2-3 weeks before surgery. The implantation of a venous access device shortly before starting bevacizumab treatment did not result in an increased incidence of bleeding or other complications (15).

Table 7. Wound healing and bleeding complications after surgery

	IFL n = 411	IFL + Bevacizumab n = 402	FU-FA + Bevacizumab n = 110
No. patients having surgery 28-60 days before Bevacizumab	180 (44%)	173 (43%)	45 (40%)
No. of bleeding events	5 (2.8%)	3 (1.7%)	1 (2.2%)
No. of wound healing events	0 (0%)	3 (1.7%)	0 (0%)

Table 8. Wound healing and bleeding complications during bevacizumab therapy (17)

	IFL n = 411	IFL + Bevacizumab n = 402	FU-FA + Bevacizumab n = 110
No patients having surgery during Bevacizumab therapy	25 (6%)	40 (10%)	15 (13%)
No. complications	0 (0%)	4 (10%)*	3 (20%)*

* include: anastomatic wound dehiscence, thoracotomy wound dehiscence, hemothorax following lung resection, ecchymosis and bleeding at colostomy site

Recommendations

1. Bevacizumab therapy should not be started for at least 4 weeks following surgery or until the wound is fully healed. If systemic treatment is deemed necessary before this period, chemotherapy can be commenced first and bevacizumab added after 4 weeks.
2. For patients on bevacizumab who require elective major surgical procedures, bevacizumab should be stopped for at least 6-8 weeks before surgery. However, chemotherapy alone can be continued until 2-3 weeks before surgery.
3. Minor surgical procedures, such as insertion of venous access devices, can be done within 7 days of bevacizumab treatment.
4. If an emergency surgical procedure is necessary during bevacizumab therapy, the risk of wound complications must be recognized and appropriate measures taken to minimize these.
5. Discontinue bevacizumab if any wound complication (fistula, dehiscence) develops or if there is intra-abdominal abscess.

GI Perforation

A serious complication of bevacizumab is GI perforation. This occurs infrequently (1.4-2.3%), but can be life-threatening with a mortality rate of 0.4-1% (2,3,16). Perforation occurs within the first 60 days of treatment in 68% of patients. Potential risk factors for perforation include acute diverticulitis, obstruction, abdominal carcinomatosis, tumor necrosis and previous pelvic/abdominal radiation. Invasive procedures (GI endoscopy), peptic ulcer disease, diverticulosis or chronic ASA (>325 mg/day)/NSAIDs usage may add to the risk of GI perforation, but this is unclear at present.

Recommendations

- 1. Patients with acute diverticulitis, obstruction, abdominal carcinomatosis, un-resected colorectal primary tumors or with a history of previous pelvis/abdominal radiation are at an increased risk for GI perforation and must be monitored for early symptoms and signs of a perforation. If a GI perforation develops, bevacizumab should be discontinued.*
- 2. Take care in patients with diverticulosis or those on chronic ASA/NSAIDs or who had GI endoscopic procedure within 3 months*
- 3. GI perforation may be managed according to its severity, and surgical intervention should be considered when appropriate, recognizing the increased risk for wound complications during bevacizumab therapy.*
- 4. Patients with active peptic ulcer disease should be treated with a proton pump inhibitor (PPI) or an H-2 blocker while on bevacizumab treatment.*
- 5. GI endoscopic procedures should be delayed, if possible, until after bevacizumab treatment.*

Reversible posterior leukoencephalopathy syndrome (RPLS)

This is a neurological syndrome which can occur rarely in patients treated with bevacizumab. The symptoms/signs are seizures, headaches, altered mental status, visual disturbance or cortical blindness. It may or may not be associated with hypertension. The syndrome can be confirmed by imaging studies. Bevacizumab should be discontinued, and concomitant hypertension treated.

Recommendations

In the event of reversible posterior leukoencephalopathy syndrome, bevacizumab should be discontinued. Specific symptoms (e.g. headaches or seizures) should be treated and concomitant hypertension, if present, controlled as outline above.

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1. Table 8. Summary of clinical management of adverse events due to bevacizumab in colorectal cancer patients

Adverse event	Precautions/monitoring	Management/therapy
Hypertension	<p>Eligibility</p> <ol style="list-style-type: none"> 1. Blood pressure <160/100 2. On stable antihypertensive medications <p>Monitoring</p> <ol style="list-style-type: none"> 1. During the first three cycles of bevacizumab therapy, check blood pressure before treatment, midway during treatment, and at end of treatment 2. Check blood pressure every 2-3 weeks during treatment 	<ol style="list-style-type: none"> 1. If acute rise in blood pressure (increase by >20 mmHg diastolic or >160/100 if previously WNL) occurs during infusion, stop and restart at slower rate if blood pressure returns to baseline level within 1 hour. If hypertension is symptomatic or grade 3 hypertension persists >1 hour, start therapy with labetalol (if pulse >65) or hydralazine (if pulse <65). Cardiology or ER consultation suggested 2. Grade 1: Continue bevacizumab. No specific therapy required. 3. Grade 2: Stop bevacizumab temporarily and start oral antihypertensive drugs; bevacizumab can be resumed when hypertension is controlled or blood pressure <160/100 Grade 3: Stop bevacizumab until blood pressure controlled by antihypertensive drugs. If uncontrolled after one month, discontinue bevacizumab 4. Hypertensive crisis: Discontinue bevacizumab
Proteinuria	<p>Eligibility</p> <ol style="list-style-type: none"> 1. Urinalysis by dipstick shows no proteinuria or 1+ proteinuria 2. If dipstick urinalysis shows \geq 2+ proteinuria, 24-hour urine for protein must be \leq 2g <p>Monitoring</p> <ol style="list-style-type: none"> 1. Monitor by dipstick urinalysis before each cycle 2. If >2+ proteinuria on dipstick urinalysis, check 24-hour urinary protein 	<ol style="list-style-type: none"> 1. 1+ proteinuria (dipstick): Continue bevacizumab 2. Proteinuria <2g (24-h urine): Continue bevacizumab and monitor 24-hour urine protein. If 24-h urine protein decreases to < 1g, resume monitoring by dipstick 3. Proteinuria > 2g (24-h urine): Hold bevacizumab and recheck before next cycle. Resume bevacizumab if proteinuria decreases to <2g. If not <2 g after 3 months, stop bevacizumab 4. Nephrotic syndrome: Discontinue Bevacizumab
Bleeding	<ol style="list-style-type: none"> 1. Take history for bleeding on each visit 2. Exercise caution in patients with coagulopathy or on full-dose anticoagulant therapy before bevacizumab 3. Do not use in patients with untreated brain metastases 	<ol style="list-style-type: none"> 1. Grade 1 or 2: Implement first-aid or medical measures as appropriate. Continue bevacizumab 2. Grade 3 or 4: Discontinue bevacizumab

Adverse event	Precautions/monitoring	Management/therapy
Venous thromboembolic events	Check clinically for development of DVT	<ol style="list-style-type: none"> Grade 3 or incidentally discovered pulmonary embolus: Stop bevacizumab for 2 weeks until full anticoagulation established Grade 4 (pulmonary embolism): Stop bevacizumab and start anticoagulant therapy. Bevacizumab may be resumed if patient is stable and full anticoagulation established Discontinue bevacizumab if any life-threatening thromboembolic event occurs
Arterial thromboembolic events	<ol style="list-style-type: none"> Exercise caution in patients with a previous history of arterial thromboembolism or over 65 years of age Withhold bevacizumab in patients with thromboembolic event within past 6 months, and start only if stable and asymptomatic 	<ol style="list-style-type: none"> Prophylactic low-dose ASA may be considered in suitable high-risk patients Discontinue bevacizumab for any arterial thromboembolic event
Wound complications	<ol style="list-style-type: none"> Delay start of bevacizumab for at least 28 days following surgery or until wound is fully healed For elective surgery during bevacizumab therapy, wait for at least 6-8 weeks after stopping bevacizumab For emergency surgery during bevacizumab therapy, monitor for wound complications (delayed healing, dehiscence or bleeding) 	<ol style="list-style-type: none"> Hold bevacizumab for any wound complications until fully resolved Discontinue bevacizumab if fistula develops Discontinue bevacizumab if wound dehiscence occurs Discontinue bevacizumab if intra-abdominal abscess develops
GI perforation	<ol style="list-style-type: none"> Take caution in patients with diverticulitis, obstruction, abdominal carcinomatosis, unresected colorectal primary tumor or previous pelvic/abdominal radiation Take care in patients with peptic ulcer disease, diverticulosis, endoscopic procedure within 3 months or those on chronic ASA/NSAIDs Monitor all patients for symptoms/signs of perforation (pain, fever, peritonitis) 	<ol style="list-style-type: none"> If GI perforation occurs, discontinue bevacizumab. Manage perforation according to severity: <ol style="list-style-type: none"> Careful observation with conservative measures (fluids, antibiotics) Surgical intervention (Caution: high risk of wound complications) Treat with PPI or H2 blocker if peptic ulcer disease present Avoid GI endoscopic procedures, if possible
Reversible leuko-encephalopathy syndrome	Monitor for symptoms/signs: seizures, headaches, altered mental status, visual disturbance, cortical blindness	<ol style="list-style-type: none"> Discontinue bevacizumab Treat specific symptoms (e.g. seizures) Control concomitant hypertension, if present