Guideline Resource Unit
guru@ahs.ca

Bevacizumab Administration

Accompanies: Clinical Practice Guideline GI-003

Cancer Care Alberta

www.ahs.ca/guru

The assessment, prevention, rehabilitation and management strategies outlined in this summary and accompanying guideline apply to adult cancer patients with advanced colorectal cancer. Refer to the full clinical practice guideline for a detailed description of the clinical questions, recommendations, guideline development methodology, and references.

Background

This resource has been created to ensure the safe administration of bevacizumab to patients with advanced colorectal cancer in Alberta. It supplements the training you have already received to deliver cytotoxic therapy.

Vascular endothelial growth factor (VEGF) is a substance that promotes angiogenesis (blood vessel growth). Bevacizumab is a monoclonal antibody directed that neutralizes VEGF; by reducing VEGF, it is thought to help "prune" the abnormal blood vessels within a tumour and to optimize the delivery of chemotherapy to the tumour. In patients with colorectal cancer, it can add to the survival advantage offered by chemotherapy alone.

Currently, bevacizumab is not administered as a single agent: it is always administered with chemotherapy. If the bevacizumab is held, however, the chemotherapy may continue under standard parameters.

Administration

Bevacizumab must be diluted in normal saline (not a dextrose-containing solution). Please refer to the AHS Provincial Parenteral Manual for further administration instructions.

Contraindications

Bevacizumab is ***contraindicated*** in patients with:

- Radiological or clinical evidence of tumour invasion into major blood vessels
- Major surgical procedure or significant traumatic injury within the past twenty-eight days
- Major surgical procedure anticipated within the following four to six weeks
- Uncontrolled hypertension
- Clinically significant cardiovascular or cerebrovascular disease (e.g., myocardial infarction or cerebrovascular accident within six months, unstable angina, congestive heart failure, use of a thrombolytic agent within the last six months, serious dysrhythmia)
- Inherited bleeding diathesis or coagulopathy with an increased risk of bleeding
- Significant pre-existing proteinuria or renal dysfunction
- Non-healing wound, ulcer, or bone fracture
- Known esophageal varices or significant ophthalmologic abnormalities
- Pregnancy, lactation, or childbearing potential without an effective method of contraception
- Untreated metastases within the central nervous system

Age over 65 years and prior arterial thromboembolic disease (e.g., myocardial infarction, cerebrovascular accident) confer a higher risk of arterial thromboembolic disease.

Adverse Events

Standard monitoring for adverse effects should occur through each cycle. The following adverse effects warrant specific attention:

Hypertension: Before issuing orders to pharmacy to prepare the bevacizumab infusion, obtain and record the patient's blood pressure.

Grade 1 Hypertension	Grade 2 Hypertension	Grade 3 Hypertension	Grade 4 Hypertension
Describes an asymptomatic or transient (<24h) rise in the diastolic blood pressure by >20 mmHg or in the blood pressure to over 150/100 if previously within normal limits.	Describes a persistent (≥24h) or symptomatic rise in the diastolic blood pressure by >20 mmHg or in the blood pressure to over 150/100 if previously within normal limits.	Describes the need to introduce more intensive therapy (e.g., addition of another anti-hypertensive agent).	Describes a rise in the blood pressure with life threatening consequences ("hypertensive crisis"). This is characterized by end-organ toxicity (e.g.: angina, headaches, reduced level of consciousness, etc.).
Continue with the bevacizumab infusion.	Initiate an anti-hypertensive medication and resume the bevacizumab only if the blood pressure remains controlled under 160/100.	Add another anti-hypertensive agent and withhold the bevacizumab until adequate control of the blood pressure is achieved.	Obtain urgent intervention (e.g., ICU/CCU for labetalol, hydralazine, nitroprusside, cardiac monitoring, etc.). Permanently discontinue the bevacizumab.

Bleeding:

Grade 1 Bleeding	Grade 2 Bleeding	Grade 3 Bleeding	Grade 4 Bleeding
Mild bleeding but intervention not indicated.	Symptomatic bleeding and minor medical intervention indicated (e.g., first-aid, cauterization).	Intervention required (e.g., transfusion, endoscopic procedure, surgery).	Urgent intervention required to manage life threatening consequences.
Continue with the bevacizumab.	Continue with the bevacizumab.	Withhold the bevacizumab and resume when no bleeding persists.	Permanently discontinue the bevacizumab.

Proteinuria: Before issuing orders to pharmacy to prepare the bevacizumab infusion, obtain a urinalysis.

Grade 1 Proteinuria	Grade 2 Proteinuria	Grade 3 Proteinuria	Grade 4 Proteinuria
1+ protein on urinalysis (*or* 0.15 to 1.0 g of protein in a 24h urine collection)	2+/3+ protein on urinalysis (*or* 1.0 to 3.5 g of protein in a 24h urine collection)	4+ protein on urinalysis (*or* over 3.5 g of protein in a 24h urine collection)	Nephrotic syndrome (over 3.5 g of protein in a 24h urine collection *plus* edema and hypertension).
Continue with bevacizumab and monitor the urine protein levels by urinalysis.	Continue with bevacizumab but obtain a 24h urine collection for protein before the patient's *next* treatment.	Withhold bevacizumab and obtain a 24h urine collection for protein before the patient's *next* treatment.	Permanently discontinue the bevacizumab.

	If the 24h urine collection for protein retrieves < 1 g, proceed with bevacizumab and resume monitoring with urinalysis. If the 24h urine collection for protein retrieves ≥ 2 g, monitor with 24h collection and resume bevacizumab only if < 2 g.	

Venous and Arterial Thromboembolic Events, including Myocardial Infarction and Cerebrovascular Accident:

Grade 1 VTE	Grade 2 VTE	Grade 3 VTE	Grade 4 VTE
Not applicable.	Deep vein thrombosis but intervention not indicated.	Deep vein thrombosis and intervention required (e.g., anti-coagulation, thrombolysis, placement of an intravascular filter, surgery).	Potentially life threatening embolic event (e.g., pulmonary embolism).
Not applicable.	Continue with the bevacizumab.	Withhold the bevacizumab.	Withhold the bevacizumab.
		Consider resuming bevacizumab once adequate anti-coagulation is established and if no hemorrhagic/ bleeding complications persist.	

Grade 1 Arterial Embolism	Grade 2 Arterial Embolism	Grade 3 Arterial Embolism	Grade 4 Arterial Embolism
Coronary Arteries Asymptomatic arterial narrowing without ischemia.	Asymptomatic but testing suggests ischemia. Stable angina.	Symptomatic and testing suggests ischemia. Unstable angina.	Acute myocardial infarction.
Cerebrovascular Arteries Not applicable.	Asymptomatic arterial narrowing without ischemia.	Transient ischemic event that lasts ≤24h.	Cerebrovascular accident with neurologic deficit that lasts >24h.
Peripheral Arteries Not applicable.	Brief (<24h) episode of limb ischemia managed non-surgically and without permanent deficit.	Recurrent or prolonged (≥24h) episode of limb ischemia. Invasive intervention indicated.	Life threatening, disabling, and/or associated with end-organ damage (e.g., loss of a limb).
Not applicable.	Permanently discontinue the bevacizumab.	Permanently discontinue the bevacizumab.	Permanently discontinue the bevacizumab.

Gastrointestinal Perforation: The risk of gastrointestinal perforation is about 2%. Risk factors include an unresected primary, obstruction, previous abdominal or pelvic irradiation, intra-abdominal carcinomatosis, peptic ulcer disease, and diverticular disease. Surgical intervention may be required.

Wound Healing Complications and Dehiscence: Bevacizumab has a half-life of about twenty days. To reduce its impact on wound healing, Bevacizumab should not be initiated within twenty-eight days

of a major surgical procedure or significant traumatic injury. It should also be withheld for at least twenty-eight days prior to an anticipated major surgical procedure.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS is characterized by seizures, lethargy, somnolence, restlessness and agitation, impaired memory and concentration, visual changes, headache, weakness, and/or incoordination. It is reversible (symptoms usually resolve within days) if recognized early and the bevacizumab promptly discontinued. If suspected, obtain a MR brain to confirm the diagnosis (the MR reveals edema in the white matter of the posterior cerebral hemispheres).

Thank you for your assistance with this patient's care. Please remember that any questions or concerns can be directed to the prescribing medical oncologist.

References

Lexicomp®. Bevacizumab. Updated 02/01/2023; accessed 02/02/2023.

Lippincott Advisor. Bevacizumab. Accessed 02/02/2023.

Abbreviations

CCU, critical care unit; ICU, intensive care unit; MR, magnetic resonance imaging; RPLS, reversible posterior leukoencephalopathy syndrome; VEGF, vascular endothelial growth factor; VTE, venous thrombosis.