Bevacizumab (in combination with chemotherapy for colorectal cancer)

Indication

For treatment of metastatic or locally advanced and inoperable colorectal cancer in first and second line treatment setting in combination with chemotherapy.
For 3rd/subsequent line treatment in combination with trifluridine & tipiracil (Lonsurf) for patients with either metastatic or locally advanced and inoperable colorectal cancer who have received 2 or more prior anticancer treatment regimens including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapies with or without anti-VEGF agents and/or anti-EGFR-based agents.

Regimen details

Given alongside 14- or 28-day cycle chemotherapy regime (see relevant separate chemotherapy protocol)

Bevacizumab 5mg/kg in 100ml sodium chloride 0.9%

Given alongside 21-day cycle chemotherapy regime (see relevant separate chemotherapy protocol)

Bevacizumab 7.5mg/kg in 100ml sodium chloride 0.9%

Cycle frequency

Every 2 or 3 weeks (depending on chemotherapy regimen)

Number of cycles

Give until disease progression or unacceptable toxicity
If treatment with chemotherapy is discontinued for any reason, then bevacizumab must also be discontinued

Administration

Give first dose over 90 minutes, second dose over 60 minutes and subsequent doses over 30 minutes if tolerated

Check blood pressure before infusion. Be aware of 'white coat syndrome' which can elevate BP.

Pre-medication

None

Emetogenicity

Minimal

Additional supportive medication

None

Extravasation

Neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Blood pressure	14 days
Urine dipstick for proteinuria	14 days

Pre-existing blood pressure must be controlled before starting treatment

Prior radiotherapy is a risk factor for the development of fistulae

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension, history of aneurysm, or dissection.

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), blood pressure, urine dipstick for proteinuria

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

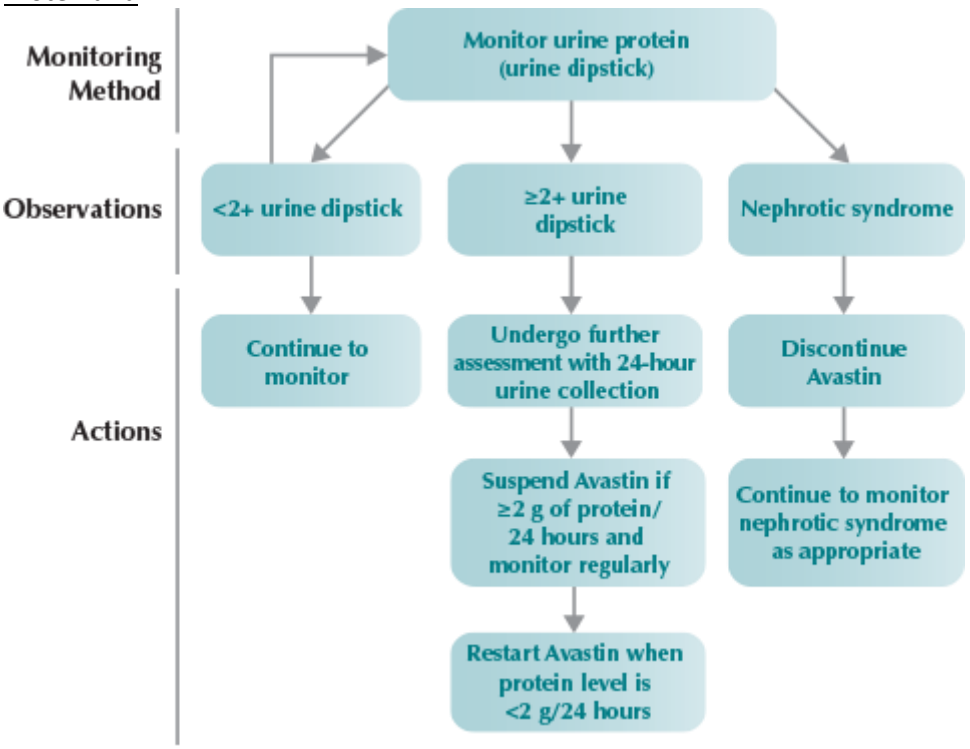
Note investigations refer to bevacizumab only. If given with chemotherapy, please refer to the relevant chemotherapy protocol	
Investigation	**Limit**
Neutrophil count	≥ 0.5 x 10^9/L
Platelet count	≥ 50 x 10^9/L
Bilirubin	≤ 1.5 x ULN
Hb	≥ 95 g/L
Blood pressure	<140/90 mmHg
Consider omitting bevacizumab rather than deferring bevacizumab where it might create problems with aligning with the next cycle of chemotherapy	
If only Hb is low (below 95g/dl) please contact doctor to arrange for blood transfusion but continue with treatment	

Dose modifications

Do not reduce the dose of bevacizumab. Dosing should be interrupted or discontinued as described below

Toxicity	Grade	Dose adjustment
Infusion related reactions	Grade ≤2	90 minute infusion: continue with dose as normal, but give premedication (paracetamol and chlorphenamine) with the next dose and give over 90 minutes. If well tolerated subsequent infusions can be reduced by 30 minutes as long as use premedication.
		60 minute infusion: all subsequent doses should be given over 90 minutes (with pre-medication)
		30 minute infusion: all subsequent doses should be given over 60 minutes (with pre-medication)
	Grade ≥2	Discontinue permanently
Proteinuria (on dipstick)	<2	Continue with bevacizumab as normal
	≥2+	See algorithm below
	Nephrotic syndrome	Permanently discontinue
Gastro-intestinal perforation or dehiscence		Discontinue permanently
Wound healing complications		Bevacizumab should not be initiated for at least 28 days following surgery or until wound is fully healed Bevacizumab should be withheld for 42 days (6 weeks) prior to elective surgery If would healing complications occur during treatment it should be withheld until the wound is fully healed.
Fistula or intra-abdominal abscess		Discontinue permanently
Venous thromboembolic event	Grade 3 Deep DVT or cardiac thrombosis needing anticoagulation or incidental first PE	Hold bevacizumab for 2 weeks May be resumed after initiation of therapeutic dose anticoagulant
	Grade 4 Embolic event including PE with life-threatening thrombus	Discontinue permanently
Arterial thrombotic event	ANY grade	Permanently discontinue
Haemorrhage	Grade 1 or 2	No modification but institute appropriate treatment
	Grade 3 or 4	Discontinue and institute appropriate treatment

Proteinuria



Hypertension

	Definition	**Action**
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously normal.	Recheck BP 1 hour later If BP <140/90 mmHg: administer as normal If BP 140/90-150/100 mmHg administer but recheck BP 48 hours later If >150/100 mmHg omit bevacizumab and recheck BP 48 hours later If BP after 48 hours still >140/90 mmHg commence antihypertensive therapy
Grade 2	Recurrent or persistent (>24 hour) increase by 20 mmHg (diastolic) or to >140/90 mmHg if previously normal	Anti-hypertensive therapy should be commenced. Once controlled to <140/90 mmHg bevacizumab can be continued
Grade 3	Requiring more than one antihypertensive or more intensive therapy than previously	Withold bevacizumab for persistent hypertension >140/90 mmHg If hypertension cannot be controlled, discontinue permanently
Grade 4	Life threatening (hypertensive crisis)	Medical emergency Permanently discontinue

Adverse effects –

for full details consult product literature/ reference texts

Fistulae and perforations
Wound healing complications
Hypertension
Posterior Reversible Encephalopathy Syndrome (PRES)
Proteinuria
Arterial thromboembolism
Venous thromboembolism
Haemorrhage
Aneurysms and artery dissections
Congestive heart failure (CHF)
Neutropenia and infections
Hypersensitivity and infusion reactions

References

Bevacizumab SPC - https://www.medicines.org.uk/emc/product/3885

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON, DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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