Bevacizumab

Indication

First or second or third line treatment of advanced colorectal cancer, in combination with oxaliplatin-based combination chemotherapy.

First line treatment of advanced colorectal cancer, in combination with irinotecan based combination chemotherapy.

First line treatment of advanced colorectal cancer in combination with a fluoropyrimidine for patients assessed as unfit to receive oxaliplatin or irinotecan based combination chemotherapy.

Not NICE approved, funding needs to be agreed prior to commencing treatment.

ICD-10 codes

Codes prefixed with C18, C19, C20.

Regimen details

Day	Drug	Dose	Frequency*	Route
1	Bevacizumab	5mg/kg	TWO WEEKLY	IV infusion
or				
1	Bevacizumab	7.5mg/kg	THREE WEEKLY	IV infusion

* The two weekly schedule is used with fluorouracil-based regimens and the three weekly schedule is used with the capecitabine-based regimens.

Cycle frequency

14 or 21 days (see above).

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Bevacizumab is administered as an intravenous infusion in sodium chloride 0.9% to a final concentration of between 1.4 to 16.5mg/mL. Doses up to 1650mg are administered in 100mL sodium chloride 0.9%, doses greater than 1650mg are administered in 250mL sodium chloride 0.9%.

Bevacizumab may be administered before or after chemotherapy.

The first infusion must be given over 90 minutes. If tolerated, the next infusion can be given over 60 minutes; if this is also tolerated, subsequent infusions can be given over 30 minutes.

Patients should be monitored for infusion related reactions and facilities must be available for resuscitation and the treatment of anaphylaxis. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy; the infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions such as hypotension, dyspnoea, angioedema or generalised urticaria require immediate discontinuation of bevacizumab and management with appropriate therapy. Paracetamol may be used.

Bevacizumab should not be initiated for at least 35 days following major surgery or until the wound is fully healed. For elective surgery, bevacizumab should be withheld for 35 days. For minor surgery (including port placement) bevacizumab should be withheld for 7 days following surgery.

Pre-medication

None routinely.
If a patient experiences a mild infusion related reaction, for future doses the patient may be prescribed paracetamol 1g PO and chlorphenamine 10mg IV.

Emetogenicity

This regimen has low emetogenic potential

Additional supportive medication

None usually required.
Antihypertensives may be required to manage hypertension commonly observed with bevacizumab therapy.

Extravasation

Bevacizumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days
Blood pressure (BP)	on day 1
Proteinuria (dipstick)	on day 1

Cardiac assessment is also required with ECHO for patients with significant cardiac history or prior chest wall radiation or anthracycline treatment.
Pre-existing hypertension should be adequately controlled before commencing treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period**
Blood pressure	Before each dose (more frequently if hypertension)
Proteinuria (dipstick)	Before each dose*

* If 3+ on dipstick perform 24 hour urinalysis and delay until <2g/24 hours.

Standard limits for administration to go ahead

As above

Dose modifications

Dose reduction is not recommended; treatment should be withheld or discontinued.

- **Haematological toxicity**

No dose modification required.

- **Renal impairment**

There is no data of administering bevacizumab in patients with renal impairment and dose modification should not be required. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

- **Hepatic impairment**

There is no data of administering bevacizumab in patients with hepatic impairment and dose modification should not be required. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Infusion related reactions	Grade ≤ 2	**90 minute infusion**: premedication prior to next dose and give over 90 minutes (if tolerated may reduce infusion duration for future cycles with premedication) **60 minute infusion**: all subsequent doses should be given over 90 minutes with premedication. **30 minute infusion**: all subsequent doses should be given over 60 minutes with premedication.
	Grade >2	Discontinue bevacizumab
Hypertension	Grade 1 Increase of >20 mmHg (diastolic) or >140/90 mmHg (previously within normal limits) asymptomatic and transient (<24 hours)	Recheck 1 hour later: - if <140/90 mmHg – administer as normal - if 140/90 mmHg - 150/100 mmHg –administer and recheck BP 48 hours later (commence antihypertensives if BP remains >140/90 mmHg). - if >150/100 mmHg – omit and recheck BP 48 hours later(commence antihypertensives if BP remains >140/90 mmHg).
	Grade 2 Recurrent or persistent (> 24 hours) increase by 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits	Withhold bevacizumab. Commence antihypertensive medication. Once BP <140/90 mmHg restart treatment.
	Grade 3 Persistent BP > 140/90mmHg, requiring increase in antihypertensive treatment	Withhold bevacizumab. If hypertension cannot be controlled permanently discontinue treatment.
	Grade 4 Hypertensive crisis	Permanently discontinue bevacizumab.
Proteinuria	1+ or 2+	Continue bevacizumab.
	3+	Continue bevacizumab, with 24 hour urinalysis prior to next cycle, then: - if <2g continue treatment with 24 hour urinalysis prior to each dose. If falls to <1g return to dipstick analysis. - if ≥2g withhold until repeat urinalysis <2g then restart treatment with 24 hour urinalysis prior to each dose.
	4+	Withhold bevacizumab. 24 hour urinalysis. Then treat as above.
	Nephrotic syndrome	Permanently discontinue bevacizumab

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Infusion related toxicity
Arterial/venous thromboembolism
GI perforation, fistulas
Haemorrhage
Pneumonitis
Osteonecrosis of the jaw
Reversible posterior leukoencephalopathy
Congestive heart failure
Wound healing complications

- **Frequently occurring side effects**

Hypertension
Proteinuria
Headache
Fatigue
Diarrhoea
Nausea and vomiting
Infections
Abdominal pain

- **Other side effects**

Nil

Significant drug interactions – for full details consult product literature/ reference texts

No documented significant reactions.

Additional comments

Bevacizumab is contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies.

Bevacizumab should be used with caution in patients with:
• Untreated central nervous system metastases
• History or risk factors for thromboembolic events
• Significant cardiac risk factors for development of congestive heart failure

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References

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- NHS England Cancer Drug Fund List. Accessed 17 July 2014 via www.england.nhs.uk
- Summary of Product Characteristics - Bevacizumab (Roche) accessed 17 July 2014 via www.medicines.org.uk

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