Systemic Anti Cancer Treatment Protocol

BEVACIZUMAB (Avastin) Gynaecological Cancer

PROCTOCOL REF: MPHAGYNBEV
(Version No: 1.1)

Approved for use in:

- First line treatment for advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer where all the CDF criteria are met
- First line treatment of recurrent or metastatic cervical cancer in combination with chemotherapy where all the CDF criteria are met

Must be registered on blueteq as funded by the Cancer Drugs Fund (CDF).

Dosage:

Chemotherapy naïve advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer

Drug	Dosage	Route	Frequency
Bevacizumab	7.5mg/kg IV (with Carboplatin and Paclitaxel)	Intravenous Infusion	3 weekly*

***Maximum 18 cycles of bevacizumab**

OR first line treatment of recurrent or metastatic cervical cancer in combination with chemotherapy

Drug	Dosage	Route	Frequency
Bevacizumab	15mg/kg IV (with Carboplatin/Cisplatin and Paclitaxel)	Intravenous Infusion	3 weekly

Supportive Treatments: None required

Interactions:

There are no known drug interactions with non-antineoplastic medications.

Extravasation risk

Bevacizumab – neutral

Refer to the network guidance for the prevention and management of extravasation

Administration

Bevacizumab may be administered before or after chemotherapy.

Day	Drug	Dose	Route	Diluent and rate
1	Sodium Chloride 0.9%	50mL	IV Infusion	Flush
1	Bevacizumab	7.5mg/kg or 15mg/kg	IV Infusion	100ml Sodium Chloride 0.9% over 30 to 90minutes*
1	Sodium Chloride 0.9%	100mL	IV Infusion	Flush

*The initial dose should be given as an intravenous infusion over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

If a patient experiences a **mild infusion-related reaction**, give future doses with premedication with paracetamol 1000mg orally and IV chlorphenamine 10mg. If the patient still experiences an infusion-related reaction, consider increasing the infusion time back up to 60 minutes or 90 minutes, as appropriate.

Comments: Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be withheld for at least 28 – 60 days before elective surgery.

For minor surgery, including port placement, it is recommended that bevacizumab is withheld for 7 days after surgery.

Main Toxicities

Bevacizumab	
Cardiac	Congestive heart failure, supraventricular tachycardia
Gastrointestinal	Rectal haemorrhage, stomatitis, constipation, diarrhoea, nausea, vomiting, abdominal pain, gastrointestinal perforation, ileus, intestinal obstruction, recto-vaginal fistulae Prior radiation is a risk factor for GI perforation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.
General Disorders	Asthenia, fatigue, pyrexia, pain, mucosal inflammation
Haematological	Febrile neutropenia, thrombocytopenia. Increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy
Musculoskeletal	Arthralgia, myalgia, muscular weakness, back pain
Nervous system	Peripheral sensory neuropathy, cerebrovascular accident, syncope, somnolence, headache
Renal	Dose dependent proteinuria is very common. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)
Reproductive	Bevacizumab may impair female fertility.
Skin	Very common: Wound healing complications, exfoliative dermatitis, dry skin, skin discoloration
Vascular	Increased risk of dose dependent hypertension. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Monitoring of blood pressure is generally recommended during therapy.
Thromboembolism	Increased risk of thromboembolic reactions including venous thromboembolism, pulmonary embolism, cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) Patients, with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients with bevacizumab. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored

Investigations

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Ongoing
Medical Assessment	X				X			X	After 3 and 6 cycles during chemo, then every 4 cycles and at the end of treatment for ovarian ca
SACT Assessment	X	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X		Every cycle, then every 3 months once chemotherapy is complete
U&E & LFT	X	X	X	X	X	X	X		Every cycle, then every 3 months once chemotherapy is complete
CrCl	X	X	X	X	X	X	X	X	Every cycle
Blood Pressure	X	X	X	X	X	X	X	X	Every Cycle
Urine Dipstick	X	X	X	X	X	X	X	X	Every Cycle
CA125*	X	X	X	X	X	X	X	X	Every cycle *ovarian patients only
CT scan	X				X			X	After 3 and 6 cycles
Informed Consent	X								
PS recorded	X	X	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Dose reduction is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Hypertension

Baseline blood pressure should be < 150/100mmHg. Pre-existing hypertension should be adequately controlled (usually by GP) before starting bevacizumab treatment.

If diastolic increase > 20mmHg above baseline or blood pressure rises to > 150/100mmHg, antihypertensive therapy may be required. Treatment, and initial monitoring until stabilized, is usually best managed via the patient's GP.

If blood pressure > 180/110mmHg, it is advised that bevacizumab therapy is withheld until blood pressure controlled.

For "white coat syndrome" induced hypertension, please contact patient's GP for monitoring of blood pressure in between cycles.

Proteinuria

1+ or 2+ on dipstick (0.3 – 2.9g/L)	3+ on dipstick (3 - 19g/L):	4+ on dipstick (≥20g/L)
Continue with bevacizumab. No additional evaluation required	May have dose of bevacizumab as scheduled, but will need 24 hour urine collection to measure protein a few days before next cycle due. If 24hr protein result < 2g, continue with bevacizumab. With continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to < 1g/24hr, return to dipstick analysis. If ≥2g, withhold bevacizumab until repeat 24 hour urine collection shows < 2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.	**Withhold bevacizumab**. 24 hour urine collection required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Hepatic Impairment There is no data for bevacizumab in patients with impaired liver function.

Renal Impairment There is no data for bevacizumab in patients with impaired renal function.

References

http://www.medicines.org.uk

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)

Stockley's drug interactions. Ninth edition. Edited K. Baxter. Pharmaceutical press. London. 2010

Roche management plan

GOG-0218 study: Incorporation of bevacizumab in the primary treatment of ovarian cancer. NEJM 2011 365:2473-2483

GOG-0240 study: Bevacizumab for advanced cervical cancer
Lancet Oncology 2015