PROTOCOL

Systemic Anti Cancer Therapy Protocol

Bevacizumab

Neurofibromatosis type ii (NF2)

PROTOCOL REF: MPHABNTII
(Version No. 1.0)

Approved for use in:

Neurofibromatosis type ii (NF2) patient with:

- At least one growing schwannoma with a rate of growth averaged over a 12 month period of ≥4mm by linear dimension or 60% by volume **OR** a symptomatic cystic ependymoma **OR** a growing schwannoma that does not meet growth criteria but is an imminent threat to neurological function.
- For patients aged 16 years and over with schwannomas that meet growth criteria and symptomatic cystic ependymomas, at least two NF2 MDTs must confirm that eligibility criteria are met and bevacizumab treatment is appropriate.
- The potential benefits of bevacizumab outweigh the potential risks

Bevacizumab in patients with Neurofibromatosis Type 2 is managed and funded via National Specialised Commissioning

Bevacizumab is initiated at treatment dose then reduced to maintenance dose (as detailed in NF2 Specialised Commissioning Policy). These decisions are made by the NF2 MDT and are individualised, depending on patient- and disease-specific factors. Long-term treatment (> 2 years) is common. Blueteq registration is not required as this is funded via block.

Dosages

Treatment Dose

Drug	Dosage	Route	Frequency
Bevacizumab	**7.5mg/kg (Can be dose increased to 15mg/kg)**	IV Infusion	3 weekly

Maintenance Dose

Drug	Dosage	Route	Frequency
Bevacizumab	**2.5mg/kg**	IV Infusion	4 weekly

Exclusion criteria

- Evidence of tumour invading a blood vessel wall
- Major surgery, open biopsy or traumatic injury within 28 days
- Peptic ulcer disease, or on chronic daily treatment with aspirin or clopidogrel
- Bleeding diathesis
- Pregnant or lactating patient. Patients must use an effective method of contraception throughout treatment.
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products (e.g Rituximab) or other recombinant human or humanised antibodies. Discuss individual cases with consultant.

Cautions

- Pre-existing hypertension
- Pre-existing proteinuria / renal impairment
- PMH of VTE
- Recent / planned surgery:
    - Due to the adverse effect of bevacizumab on wound healing and the half-life of three weeks, it is recommended that **elective major surgery should be postponed until at least 28 days after the last dose of bevacizumab has been administered**.
    - Bevacizumab therapy should not be initiated for at least 28 days following major surgery and until the surgical wound is fully healed.
    - Emergency surgery should not be delayed and should proceed following consideration of the risks versus benefits.

For minor surgery, including port placement and dental work, it is recommended that bevacizumab is withheld as follows:

- Tunnelled CVC: For 14 days prior to insertion, and 24 hours after insertion, providing there is no bleeding at the site.
- TIVAD: For 4 weeks prior to insertion, and not to be re-started until implantation site has healed, usually 7-10 days.
- Dental work: Minor dental work (scale and polish, minor fillings): No precautions necessary

- Major dental work (risk of bleeding – extractions, root canal work etc): Allow minimum of 10 days pre and post bevacizumab, up to 28 days if possible (discuss proposed procedure with dentist).

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

Day	Drug	Dose	Route	Diluent and rate
1	**Sodium Chloride 0.9%**	**50mL**	IV Infusion	Flush
1	**Bevacizumab**	**15mg/kg , 7.5mg/kg or 2.5mg/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 and treatment plan: Induction Phase Cycles 1-3 (21 Day Cycle)

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Ongoing
Informed Consent	x								
Medical Assessment	x	x	x	x	x	x	x	x	Every cycle
SACT Assessment (to include PS and toxicities)	x	x	x	x	x	x	x	x	Every cycle
FBC	x	x	x	x	x	x	x	x	Every cycle, then every 3 months once chemotherapy complete
U&E & LFTs & Magnesium	x	x	x	x	x	x	x	x	Every cycle then every 3 months once chemotherapy complete
Crcl	x	x	x	x	x	x	x	X	Every cycle then every 3 months once chemotherapy complete
Blood Pressure	x	x	x	x	x	x	X	x	Every cycle
Urine Dipstick	x	x	x	x	x	x	x	x	Every cycle
CT/ MRI scan	x								If clinically indicated
PS Recorded	x	x	x	x	x	x	x	x	Every cycle
Toxicities documented	x	x	x	x	x	x	x	X	Every cycle
Height recorded	x								
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/

Treatment Protocol for Bevacizumab in the treatment of Neurofibromatosis II (NF2) Patients. The Christie NHS Foundation Trust. Version 1.0 March 2019.

Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.

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

Roche management plan

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
		Hugh O'Neill **Specialist Oncology Pharmacist**	New Protocol Regimen V1.0