Network
Chemotherapy Regimens
Central Nervous System
Notes from the editor

These protocols are available on the Network website www.tvcn.nhs.uk.

Any correspondence about the regimens should be addressed to:
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e-mail: sally.coutts@nhs.net
Tel: 01865 857158 to leave a message

Acknowledgements
These regimens have been compiled by the Network Pharmacy Group in collaboration with the Central Nervous System TSSG with key contribution from
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Alison Ashman, Formerly Lead Pharmacist Thames Valley Cancer Network

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Network Chemotherapy Protocols
Central Nervous System

Network Chemotherapy regimens used in the management of Central Nervous System Cancer
Date published: January 2014
Date of review: January 2016

Chemotherapy Protocols

<table>
<thead>
<tr>
<th>Name of protocol</th>
<th>Indication</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of amendments to this version</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>PCV</td>
<td>Glioma</td>
<td>5</td>
</tr>
<tr>
<td>Temozolomide 150/200</td>
<td>Glioma</td>
<td>7</td>
</tr>
<tr>
<td>Temozolomide and radiotherapy</td>
<td>Glioma</td>
<td>9</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Glioma</td>
<td>11</td>
</tr>
<tr>
<td>Vincristine + VCP</td>
<td>Medulloblastoma, PNET</td>
<td>13</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Neurofibromatosis 2</td>
<td>16</td>
</tr>
<tr>
<td>Common Toxicity Criteria</td>
<td></td>
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</tbody>
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List of amendments in this version

Protocol type: CNS Tumours
Date due for review: January 2016
Previous Version number: 4.2
This version number: 4.2a

Table 1 Amendments

<table>
<thead>
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<tbody>
<tr>
<td>13</td>
<td>Reference</td>
<td>Vincristine + VCP regimen add indication, reference and vincristine recommendation</td>
<td>Dr Blesing</td>
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<td>Temozolomide</td>
<td>hepatic impairment warning</td>
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Table 2 New protocols to be approved and added to these protocols by TSSG

<table>
<thead>
<tr>
<th>Name of protocol</th>
<th>Indication</th>
<th>Reason / Proposer</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
PCV (Glioma)

Indication: High and low grade gliomas (relapse following radiotherapy).
Anaplastic oligodendroglioma – as adjuvant following radiotherapy

DRUG REGIMEN
Day 1  PROCARBAZINE 100 mg/m²/day po in 3 divided doses (max 200 mg) for 10 days
LOMUSTINE (CCNU) 100 mg/m² once at night (max 200 mg) po day 1 only
VINCRISTINE 1.5 mg/m² (Max 2 mg) in 50ml sodium chloride 0.9% infusion over 10 minutes day 1 only

Cycle Frequency: Every 42 days up to maximum of 6 cycles

DOSE MODIFICATIONS
Previous neutropenic sepsis, discuss with Consultant or Registrar if myelosuppression at day 1, delay treatment for 2 weeks and reduce lomustine dose to 50 mg/m²

Procarbazine:
Discuss if serum creatinine is ≥ 120 micromol/L.
If serum creatinine is >177 micromol/L give 50% dose.
For severe renal impairment – not recommended.
If bilirubin > 50 micromol/L consider giving 50% dose.
If bilirubin > 85 micromol/L or AST >180iu omit.

Lomustine:
Only 40 mg capsules available
Creatinine clearance
>60ml/min give 100% dose
45-60ml/min give 75% dose
30-45ml/min give 50% dose
<30ml/min not recommended

Vinblastine:
Bilirubin 25-51 or AST 60-180u/L give 50% dose
Bilirubin >51 micromol/L and normal AST give 50% dose
Bilirubin >51 micromol/L and AST >180u/L omit
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
</tr>
</tbody>
</table>

Serum creatinine (procarbazine)

2) Non urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Drugs to be avoided concurrently with procarbazine (weak MAO inhibitor)
Alcohol, narcotic analgesics,
Drugs with anticholinergic effects (including phenothiazine derivatives and tricyclic antidepressants), other CNS depressants and antihypertensive agents.
Cimetidine should be avoided with lomustine.

ANTIEMETIC POLICY
Moderately emetogenic day 1. Antiemetics should be taken prior to lomustine –
the addition of a single dose of lorazepam 1 mg may be helpful.
Low emetogenic risk days 2 -10
* Please note: patients may already be taking dexamethasone for raised intracranial pressure

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

REFERENCES
TEMOZOLOMIDE 150/200 (Glioma)

Indications: Relapsed high grade glioma following failure of first line chemotherapy. Following concomitant Temozolomide and radiotherapy.

NICE guidance  www.nice.org.uk
- Patients with recurrent malignant glioma (brain cancer) who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy of side effects) may be considered for treatment with temozolomide.
  Such patients must have a histologically proven malignant glioma (WHO grades III and IV, or transformed grade II) at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more at initiation of temozolomide treatment.
- Temozolomide is recommended as a possible treatment for people with newly diagnosed glioblastoma multiforme who have a WHO performance status of 0 or 1.

DRUG REGIMEN
In patients previously treated with chemotherapy
Day 1  TEMOZOLOMIDE 150 mg/m² once daily for 5 days on cycle 1.
  Temozolomide hard capsules should be administered in the fasting state.
  Cycle 2 onwards the dose may be increased to 200mg/m² daily providing
  Neutrophils ≥ 1.5 x 10⁹/l and Platelet ≥ 100 x 10⁹/l on days 21 and 28 of the cycle but if
  FBC is not acceptable on day 28 then treatment should be deferred.

Cycle Frequency: Every 28 days continued according to response

DOSE MODIFICATIONS
Temozolomide available as 5 mg, 20 mg, 100 mg, 140mg, 180mg or 250 mg capsules
If neutrophils falls to < 1 x 10⁹/l or the platelet count is < 50 x 10⁹/l during any cycle,
the next cycle should be reduced one dose level. Dose levels include 150 mg/m² and 100 mg/m².
FBC should be checked on Day 21 and Day 28 on cycle 1 and at least on Day 28 for subsequent cycles.

Patients with hepatic or renal impairment
The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment. No data are available on the administration of temozolomide in patients with severe hepatic impairment (Child's Class C) or with renal impairment. Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in patients with severe hepatic impairment or any degree of renal impairment. However, caution should be exercised when temozolomide is administered in these patients.
INVESTIGATIONS

Routine Blood test

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL ≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10^9/L ≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L ≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

LFTs

2) Non-urgent tests

Tests relating to disease response/progression

CONCURRENT MEDICATION

ANTIEMETIC POLICY

Moderately emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide.

REFERENCES

1. Summary of Product Characteristics
TEMOZOLOMIDE and concomitant RADIOTHERAPY
(Glioblastoma)

*Indication:* In the first-line treatment of patients with newly diagnosed glioblastoma (GBM) as an adjunct for radiotherapy

Day 1 TEMOZOLOMIDE 75mg/m² for 7 days with concomitant radiotherapy
Day 8 TEMOZOLOMIDE 75mg/m² for 7 days with concomitant radiotherapy
Day 15 TEMOZOLOMIDE 75mg/m² for 7 days with concomitant radiotherapy
Day 22 TEMOZOLOMIDE 75mg/m² for 7 days with concomitant radiotherapy
Day 29 TEMOZOLOMIDE 75mg/m² for 7 days with concomitant radiotherapy
Day 36 TEMOZOLOMIDE 75mg/m² for 7 days with concomitant radiotherapy

Concomitant radiotherapy is 60 Gy administered in 30 fractions.

*Cycle frequency:* One cycle only (42 days in total, dispense 7 days at a time)
After a 4 week break follow with a further 6 cycles as in temozolomide 150/200 (glioma) protocol.

**DOSE MODIFICATIONS**
Temozolomide available as 5 mg, 20 mg, 100 mg, 140mg, 180mg or 250 mg capsules

No dose reductions will be made, but temozolomide may be delayed or discontinued depending on weekly haematological and non-haematological toxicity criteria. Temozolomide can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10⁹/L, platelet count ≥ 100 x 10⁹/L, Common Toxicity Criteria (CTC) non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Temozolomide interruption</th>
<th>Temozolomide discontinuation</th>
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</thead>
<tbody>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥ 0.5 and &lt; 1.5</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Platelets x 10⁹/L</td>
<td>≥ 10 and &lt; 100</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Non-haematological</td>
<td>CTC Grade 2</td>
<td>CTC Grade 3 or 4 toxicity (except for alopecia, nausea, vomiting)</td>
</tr>
</tbody>
</table>

Treatment with concomitant temozolomide can be continued when all of the following conditions are met: neutrophils ≥ 1.5 x 10⁹/L; platelets ≥ 100 x 10⁹/L; CTC non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting).
Patients with hepatic or renal impairment

The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment. No data are available on the administration of temozolomide in patients with severe hepatic impairment (Child's Class C) or with renal impairment. Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in patients with severe hepatic impairment or any degree of renal impairment. However, caution should be exercised when temozolomide is administered in these patients.

INVESTIGATIONS

FBC required weekly
Neutrophil count ≥1.5 x 10^9/L
Platelets ≥100 x 10^9/L
LFTs prior to each cycle and midway through cycle

CONCURRENT MEDICATION

Prophylactic antibiotics – co-trimoxazole 960mg od three times a week during chemo radiotherapy or dapsone 100mg od if allergic to co-trimoxazole.

ANTI-EMETIC POLICY

Highly emetogenic
NB patients are usually already taking dexamethasone.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide. Temozolomide should be taken on an empty stomach.
Carboplatin (High grade glioma)

Indication: In the third-line treatment of fit patients with relapsed high grade glioma

DRUG REGIMEN
Day 1 CARBOPLATIN AUC 6 in 500ml glucose 5% infusion over 60minutes

Dose (mg) = AUC x (GFR+25)

NB Ideally GFR should be measured using EDTA
If not it may be calculated

Cycle frequency: Every 4 weeks for 3 - 6 cycles

DOSE MODIFICATIONS
Discuss if patient has a serum creatinine > 150 micromol/L
If GFR/ calculated CrCl = or < 20ml/min contraindicated
Myelosuppression- if dose is delayed by 1 week or more reduce dose to AUC 5
Dose dependant on renal function.

INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

Give
Discuss
Hb x g/dL ≥10 < 10
Plt x 10^9/L ≥100 < 100
Neutrophils x 10^9/L ≥1.5 < 1.5

Serum creatinine
2) Non urgent tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.
DEXAMETHASONE 20mg IV bolus
CHLORPHENAMINE 10mg IV bolus
RANITIDINE 50mg IV bolus
Carboplatin should be given at a slower rate e.g. 2-4 hours.
ANTI-EMETIC POLICY
Moderately emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Ototoxicity - monitor
Neurotoxicity – monitor
Vincristine + VCP (Medulloblastoma)

**Indication:** Medulloblastoma and PNET with concurrent radiotherapy. Adjuvant therapy should be discussed with adult patients as there is no randomised evidence for its use.

**DRUG REGIMEN**

**Day 1**

**VINCRISTINE** 1.5 mg/m² (max 2 mg) in 50ml sodium chloride 0.9% infusion over 10 minutes

*Cycle frequency: Every 7 days for 8 doses starting the same week as RT*

*Then starting 6 weeks after radiotherapy*

**Day 1**

Pre-hydration

**CISPLATIN** 70 mg/m² in 1000ml sodium chloride 0.9% infusion over 3 hours

Post-hydration

**LOMUSTINE (CCNU)** 75 mg/m² once at night po day 1 only

**Days 1, 8 and 15 VINCRISTINE** 1.5 mg/m² (Max 2 mg) in 50ml sodium chloride 0.9% infusion over 10 minutes

*Cycle Frequency: Every 42 days for 8 cycles*

NB Lomustine dose may be escalated up to 100mg/m² may be possible for later cycles. Vincristine not recommended for low risk localised disease <1.5cm³. Check with Consultant

**DOSE MODIFICATIONS**

Previous neutropenic sepsis, discuss with Consultant or Registrar if myelosuppression at day 1, delay treatment for 2 weeks and reduce lomustine dose to 50 mg/m

**Lomustine:**

Only 40 mg capsules available

Creatinine clearance

- >60ml/min give 100% dose
- 45-60ml/min give 75% dose
- 30-45ml/min give 50% dose
- <30ml/min not recommended
**Vincristine:**

- Bilirubin 25-51 or AST 60-180u/L give 50% dose
- Bilirubin >51micromol/L and normal AST give 50% dose
- Bilirubin >51micromol/L and AST >180u/L omit

  - Epileptic seizure or ileus: Stop vincristine in this course, reduce to 1mg/m² next course.
  - After recovery give vincristine at 100% dose.

  - Significant dysaethesia: Omit vincristine until recovery. muscle weakness or abdominal pain
  - After recovery give vincristine at 100% dose.

**Cisplatin:**

- GFR > 60ml/min give 100% dose
- GFR 45-59ml/min give 75% dose
- GFR < 45ml/min consider carboplatin: If patient complains of tinnitus, tingling of fingers and/or toes discuss with SpR or Consultant before administration. Consider dose reduction to cisplatin 50mg/m².

**INVESTIGATIONS**

**Routine Blood test**

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Give</th>
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<tr>
<td>Hb x g/dL ≥10</td>
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<tr>
<td>Plt x 10⁹/L ≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L ≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>
- Serum creatinine (procarbazine)
- Monitor magnesium throughout treatment.
- GFR assessed using 51Cr-EDTA result or calculated creatinine clearance at the Consultant's discretion. 51Cr-EDTA advised if patient has not had one previously, has a calculated creatinine clearance < 60ml/min or has ascites.
- Ensure patient is passing urine well and calculated creatinine clearance is not falling with each cycle. (cisplatin)
- Ototoxic. Patients may need baseline audiometry particularly if elderly. Repeat audiometry if patient complains of hearing loss or tinnitus. (cisplatin)
- Neurotoxic. Monitor for signs of peripheral neuropathy.

2) Non urgent tests

Tests relating to disease response/progression
CONCURRENT MEDICATION
Hydration must be given pre and post cisplatin
Ensure adequate pre-and post-hydration prescribed at the end of the TVCN protocols. If urine output is < 100 ml/hour or patient gains > 2kg in weight during IV administration post Cisplatin give 20-40 mg Furosemide PO/IV or 200 ml Mannitol 10% IV

Cimetidine should be avoided with lomustine.

ANTIEMETIC POLICY
Vincristine single agent – minimal emetic risk
VCP – Highly emetogenic day 1
Antiemetics should be taken prior to lomustine the addition of a single dose of lorazepam 1 mg may be helpful.
Dexamethasone should not be used as an anti-emetic unless other therapies fail.
*Please note: patients may already be taking dexamethasone for raised intracranial pressure

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Otototoxicity – assess patient for tinnitus or hearing abnormalities.
Vincristine may cause neurotoxicity.

REFERENCES
2. www.bnos.org.uk Adult PNET rare tumour guidelines
BEVACIZUMAB 2 weekly (Neurofibromatosis 2)

**Indication: confirmed diagnosis of neurofibromatosis 2**

**Inclusion criteria**
- At least one growing schwannoma with rate of increase in diameter of >=4mm per year or 60% volumetric increase in size of the schwannoma averaged over a 12 month period AND
- The potential benefits of Bevacizumab outweigh the potential risks

**Additional criteria**
- All patients <16 years should have approval from the other 3 centres.

**Plus all of the following:-**
- WBC ≥ 2.0 x10^9/l, neutrophils ≥ 1.0 x10^9/l and platelets ≥ 100 x10^9/l
- Adequate liver function: bilirubin ≤ 1.5 x upper limit normal (ULN), AST & ALT ≤ 2.5 x ULN
- Adequate renal function: GFR (measured or calculated) ≥ 90 ml/min/1.73 m², creatinine ≤ 1.5 x ULN for age.
- No significant proteinuria: first early morning urine < 2+ protein. If ≥ 2+, early morning urine alb:creat ratio < 30 mg/mmol or prot:creat ratio < 50 mg/mmol
- INR ≤ 1.5, APTT ≤ 1.5 x ULN
- Normal blood pressure: systolic and diastolic ≤ 95th centile for for age, gender or height
- MRC assessment of gait (grade)
- 10m timed walk (document assisted/unassisted): best of 3 trials
- 6 minute walk

**Exclusion Criteria**
1. WHO performance status 3+, as the lower performance status patients are at higher risk of serious thromboembolic complications from therapy.
2. Evidence of tumour invading a blood vessel wall
3. Major surgery, open biopsy or traumatic injury within 28 days
4. Peptic ulcer disease, or on chronic daily treatment with aspirin or clopidogrel
5. Unhealed wounds or fractures
6. Bleeding diathesis
7. History of CVA, uncontrolled seizures, MI, TIA, unstable angina, arrhythmias

**NB:** may only be given where individual funding has been approved through NF2 MDT. This Unlicensed indication has been approved for use by OUH MAC (2011).
Protocol for treatment
If patients meet the criteria for treatment above.
1. Baseline toxicity investigations – see inclusion criteria – including X-ray of left hand & wrist if patient has not completed growth.
2. Offer sperm banking to male patients +/- egg or embryo storage to female patients
3. Undertake volumetric MRI with 1mm slices of target lesion and additional known intracranial and intraspinal tumours as baseline scan
4. Baseline QOL assessment
5. Within 2 weeks start bevacizumab for 6 months 5mg/kg 2 weekly. The option for the 7.5mg/kg 3 weekly regime could be considered for those who have to travel a long distance for treatment.
6. Rescan with volumetric MRI at 3 months. If increase in volume of target lesion(s) and no improvement in hearing, stop treatment otherwise continue

DRUG REGIMEN
Day 1 BEVACIZUMAB 5**mg/kg IV in 100ml sodium chloride 0.9% infusion over 90* minutes.

* The initial dose should be administered over 90 minutes, if tolerated well 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.

Cycle frequency: Repeat every 14 days, with 3 monthly scans to confirm ongoing treatment.

**The option for the 7.5mg/kg 3 weekly regimen could be considered for those who have to travel a long distance for treatment.

INVESTIGATIONS
Before each dose of bevacizumab the following criteria must be met
1. Neutrophils ≥1.0, platelets ≥ 80
2. Bilirubin ≤ 1.5 x ULN, AST & ALT ≤ 2.5 x ULN
3. GFR (measured or calculated) ≥ 90 ml/min/1.73 m², creatinine ≤ 1.5 x ULN for age.
4. No significant proteinuria: first early morning urine < 2+ protein. If ≥ 2+, early morning urine alb:creat ratio < 30 mg/mmol or prot:creat ratio < 50 mg/mmol
5. Systolic and diastolic BP ≤ 95th centile for age, gender or height
6. In addition, X-ray left hand and wrist after 6 & 12 months for growing patients still on therapy
7. QOL assessment at 0, 6 & 12 months
DOSE MODIFICATIONS (See also stopping rules below)
Renal impairment no studies have been conducted to investigate bevacizumab in renal impairment since the kidneys are not a major organ for bevacizumab metabolism or excretion. Clinical decision.

Hepatic impairment no studies have been conducted to investigate bevacizumab in hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion. Clinical decision.

Proteinuria
If ≥ 2+, check early morning urine alb:creat ratio if < 30 mg/mmol or prot:creat ratio < 50 mg/mmol go ahead. If above this stop treatment. If nephrotic syndrome stop treatment.

Hypertension.
Recurrent or persistent (>24hrs) increase to >150/100: Treat hypertension, but withhold bevacizumab until <150/100.

Tests relating to disease response/progression.
MRI every 3 months – discuss at NF2 MDT
Reassess at 6 months
1. Rescan at 6 months to include target lesion(s) and all known other tumour sites.
2. If target tumour is unchanged compared to 3-month scan consider maintenance treatment at 2.5 - 5 mg/kg 4-weekly. Otherwise cease treatment.
3. If target tumour shows further reduction in volume compared to 3-month scan continue treatment dose at 5 mg/kg 2-weekly. Scan at 3-monthly intervals. Once tumour volume becomes stable on 2 successive 3-monthly scans consider maintenance dose as above. Otherwise cease treatment.
4. If progression on 5mg per kg cease treatment
5. Scan at 3 monthly intervals whilst on treatment
6. MRC assessment of gait (grade)
7. 10m timed walk (document assisted/unassisted): best of 3 trials
8. 6 minute walk

QOL assessment at 0, 6 & 12 months
Stopping Rules
NCI CTC Grade 3+ toxicity
1. Systolic or diastolic hypertension ≥ 95th centile
2. Proteinuria – early morning urine alb:creat ratio ≥ 30 mg/mmol or prot:creat ratio ≥ 50 mg/mmol
3. Failure to meet re-treatment criteria for greater than 6 weeks following the start of the last cycle
4. Gastrointestinal perforation
5. Wound healing complications requiring medical intervention
6. Serious thrombotic episode or acute coronary episode,
7. Bleeding episode
8. Non-GI fistula formation

End of treatment assessment
1. Volumetric MRI
2. Audiological assessment
3. Baseline haematology and biochemistry
4. Early morning urine. If ≥ 2+ protein, early morning urine alb:creat ratio
5. GFR – measured or estimated
6. X-ray left hand & wrist for growing patients
7. QOL assessment

CONCURRENT MEDICATIONS

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Gastrointestinal perforation
Haemorrhage
Arterial and venous thromboembolism
Hypertension
Proteinuria
Reversible posterior leukoencepalopathy syndrome (rare)

ANTI-EMETIC POLICY
Minimal emetic risk all days

REFERENCES
3. NSCT protocol for use of Bevacizumab in Neurofibromatosis Type 2 Updated Jan 2012.
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic</strong></td>
<td>None</td>
<td>Transient rash, drug fever &lt;38°C (100.4°F)</td>
<td>Urticaria, drug fever ≥38°C (100.4°F) and/or asymptomatic bronchospasm</td>
<td>Symptomatic bronchospasm requiring parenteral medication(s) with or without urticaria; allergy related oedema / angioedema</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td><strong>Alopecia</strong></td>
<td>Normal</td>
<td>Mild hair loss</td>
<td>Pronounced hair loss</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Anorexia</strong></td>
<td>None</td>
<td>Loss of appetite</td>
<td>Oral intake significantly decreased</td>
<td>Requiring IV fluids</td>
<td>Requiring feeding tube or parenteral nutrition</td>
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<td><strong>Blood counts</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Neutrophils</td>
<td>Within normal limits</td>
<td>1.5x10⁹/L - normal</td>
<td>1.0-1.4x10⁹/L</td>
<td>0.5-0.9x10⁹/L</td>
<td>&lt;0.5x10⁹/L</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Within normal limits</td>
<td>10.0g/dl – normal</td>
<td>8.0 9.9g/dl</td>
<td>6.5-7.9g/dl</td>
<td>&lt;6.5g/dl</td>
</tr>
<tr>
<td>Platelets</td>
<td>Within normal limits</td>
<td>75x10⁹/L - normal</td>
<td>50-74x10⁹/L</td>
<td>10-49x10⁹/L</td>
<td>&lt;10x10⁹/L</td>
</tr>
<tr>
<td>White blood count</td>
<td>Within normal limits</td>
<td>3.0x10⁹/L - normal</td>
<td>2.0-2.9x10⁹/L</td>
<td>1.0-1.9x10⁹/L</td>
<td>&lt;1.0x10⁹/L</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>None</td>
<td>Mild increase in loose, watery colostomy output compared with pre-treatment</td>
<td>Moderate increase in loose, watery colostomy output compared with pre-treatment, but not interfering with normal activity</td>
<td>Severe increase in loose, watery colostomy output compared with pre-treatment, interfering with normal activity</td>
<td>Physiologic consequences requiring intensive care, or haemodynamic collapse</td>
</tr>
<tr>
<td>(patients with colostomy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>None</td>
<td>Increase of &lt;4 stools/day over pre-treatment</td>
<td>Increase of 4-6 stools/day, or nocturnal stools</td>
<td>Increase of ≥ 7 stools/day, or incontinence; or need for parenteral support for dehydration</td>
<td>Physiological consequences requiring intensive care, or haemodynamic collapse</td>
</tr>
<tr>
<td>(patients without colostomy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hand-foot skin reaction</strong></td>
<td>None</td>
<td>Skin changes or dermatitis without pain</td>
<td>Skin changes with pain, not interfering with function</td>
<td>Skin changes with pain, interfering with function</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hepatic – alk phos</strong></td>
<td>UNL</td>
<td>&gt;ULN – 2.5xULN</td>
<td>&gt;2.5 – 5.0xULN</td>
<td>5.0 – 20.0xULN</td>
<td>&gt;20.0XULN</td>
</tr>
<tr>
<td><strong>Hepatic – bilirubin</strong></td>
<td>UNL</td>
<td>&gt;ULN – 1.5xULN</td>
<td>&gt;1.5 – 3.0xULN</td>
<td>3.0 – 10.0xULN</td>
<td>&gt;10.0XULN</td>
</tr>
<tr>
<td>Symptom</td>
<td>None</td>
<td>Increased fatigue over baseline, but not altering normal activities</td>
<td>Moderate (decrease in performance status by level 1) or causing difficulty performing some activities</td>
<td>Severe (decrease in performance status by ≥2 levels), or loss of ability to perform some activities</td>
<td>Bedridden or disabling</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Lethargy</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>None</td>
<td>Able to eat</td>
<td>Oral intake significantly decreased</td>
<td>No significant intake, requiring IV fluids</td>
<td></td>
</tr>
<tr>
<td>Neuropathy - motor</td>
<td>Normal</td>
<td>Subjective weakness but no objective findings</td>
<td>Mild objective weakness interfering with function, but not interfering with activities of daily living</td>
<td>Objective weakness interfering with activities of daily living</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Neuropathy - sensory</td>
<td>Normal</td>
<td>Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function</td>
<td>Objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living</td>
<td>Sensory loss of paresthesia interfering with activities of daily living</td>
<td>Permanent sensory loss that interferes with function</td>
</tr>
<tr>
<td>Pain</td>
<td>None</td>
<td>Mild pain not interfering with function</td>
<td>Moderate pain: pain or analgesics interfering with function but not interfering with activities of daily living</td>
<td>Severe pain: pain or analgesics severely interfering with activities of daily living</td>
<td>Disabling</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>None</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>Painful erythema, oedema or ulcers but can eat or swallow</td>
<td>Painful erythema oedema, or ulcers requiring IV hydration</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>None</td>
<td>1 episode in 24 hours</td>
<td>2-5 episodes in 24 hours</td>
<td>≥6 episodes in 24 hours, or need for IV fluids</td>
<td></td>
</tr>
</tbody>
</table>

Network Chemotherapy Protocols – CNS Cancer  Page 21 of 21