Chemotherapy Protocol

Central Nervous System

CISPLATIN-LOMUSTINE-VINCRISTINE (Packer LCV3)

Regimen

- CNS – Cisplatin-Lomustine-Vincristine (Packer LCV3)

Indication

- Adjuvant treatment for medulloblastoma
- Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Lomustine	Myelosuppression, pulmonary fibrosis
Procarbazine	Rash, loss of appetite, flu like symptoms

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFT's & U&E's prior to day one of each cycle

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.
Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Prior to starting chemotherapy treatment the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Consider blood transfusion or erythropoietins if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Neutrophils / Platelets	Dose Reduction
Neutrophils less than $0.5x10^9$/L or platelets less than $100x10^9$/L	Delay chemotherapy for at least one week.
If there is a lack of count recovery after more than two weeks (neutrophils less than $0.5x10^9$/L or platelets less than $100x10^9$/L)	Give cisplatin and vincristine above (omit lomustine for that or course)
If recovered prior to next course	Reintroduce lomustine at a reduced dose of 50 mg/m^2
If neutrophils are less than $0.5x10^9$/L and episode of neutropenic fever at any time (nadir).	Reduce lomustine to 50 mg/m^2 in the next course and all subsequent courses.
If further episode of neutropenia	Reduce cisplatin to 50mg/m^2 and fever (less than $0.05x10^9$/L) in the next and subsequent courses
If the platelets are less than $30x10^9$/L and/or platelet transfusion	Reduce lomustine to 50mg/m^2 in the next course and all subsequent courses
If further episode of thrombocytopenia (platelets less than $30x10^9$/L)	Omit lomustine in the next course and all subsequent courses

Hepatic Impairment

Drug	Bilirubin (µmol/L)	AST/ALT	Dose
Cisplatin	No dose reduction necessary		
Lomustine	more than 25	and more than 5xULN	omit or dose reduce
	more than 85	or more than 5xULN	omit
Vincristine	26-51	or 60-180	50%
	more than 51	and normal	50%
	more than 51	and more than180	omit

Renal Impairment

Creatinine Clearance (ml/min)	Lomustine Dose	Cisplatin Dose
more than 60	100%	100%
45 – 60	75%	75%
30 - 45	50%	Less than 45 consider use of carboplatin
less than 30	Not recommended	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 2 toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. For toxicity that is NCI-CTC grade 3 or above discontinue treatment.

Cisplatin

High frequency hearing loss progressing to involve the speech frequency range (500-3,000 Hz) is a major toxicity of cisplatin. It is clear that the ototoxicity is dependent upon the cumulative dose of cisplatin, but other factors such as the dose per course and drug scheduling may be important. Monitoring of hearing loss during chemotherapy is a fundamental and mandatory part of clinical practice.

Brock / CTC (SIOP) Grading:

0 Loss of less than 40 db on all frequencies
1 Loss at least 40 db at 8000 Hz
2 Loss at least 40db at 4000 Hz
3 Loss at least 40 db at 2000 Hz
4 Loss at least 40 db at 1000 Hz

Grading for audiometry is based on loss in both ears, thus the grading (including that for modification of chemotherapy) is based on the lowest grading i.e. the 'best ear'.

Grade	Cisplatin Dose Modification
0-1	None
2	Substitute carboplatin 400mg/m^2 for cisplatin
3-4	Omit cisplatin

Modifications in the dose of cisplatin are also necessary for peripheral sensory and motor neurotoxicity, or nephrotoxicity. Consider stopping treatment for patients with neurotoxicity of NCI-CTC grade 3 or more.

Vincristine

Symptom	Dose
Vincristine associated seizures or ileus. Rule out SIADH as a cause of seizures	Omit vincristine during current course of chemotherapy and reduce to 1mg/m^2 (maximum 2mg) for next course. If seizures or ileus do not recur, then return to full dose
Parasthesia, weakness, abdominal pain or constipation	Omit next vincristine dose but on recovery reintroduce at a reduced dose of 1mg/m^2 (max 2mg) increasing to full dose if symptoms do not return

Regimen

42 day cycle for 6 cycles

Drug	Dose	Days	Administration
Cisplatin	70mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/min
Lomustine	75mg/m^2 once a day	1	Oral
Vincristine	1.5mg/m^2 (maximum 2mg)	1, 8, 15	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

Dose

- Cisplatin will be dose banded in accordance with the national dose bands
- Lomustine is available as 40mg capsules. The dose will be rounded to the nearest 40mg (up if halfway)
- The maximum dose of vincristine is 2mg
- Vincristine will be dose banded in accordance with the national dose bands

Administration Information

- Lomustine capsules must be swallowed whole with a glass of water and must not be opened or chewed.

Additional Therapy

Antiemetics

- 15-30 minutes prior to chemotherapy on day 1
    - aprepitant 125mg oral
    - dexamethasone 4mg oral or intravenous (omit if patient is already taking dexamethasone)
    - ondansetron 8mg oral or intravenous
- As take home anti-emetics
    - aprepitant 80mg once a day for two days starting on day 2 of the cycle oral
    - dexamethasone 4mg once a day for three days starting on day 2 of the cycle oral
    - metoclopramide 10mg three times a day for three days then 10mg three times a day when required for the relief of nausea and vomiting oral
    - ondansetron 8mg twice a day for three days oral

- Cisplatin pre and post hydration as follows;

  Pre

  Furosemide 40mg oral or intravenous

  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Post

  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.

- Ciprofloxacin 500mg twice a day for seven days starting on day 5 of the cycle oral

- Growth factor according to local formulary choice. For example;

  - filgrastim or bioequivalent 30million unit once a day subcutaneous for seven days starting on day three of the cycle
  - lenograstim or bioequivalent 33.6million unit once a day subcutaneous for seven days starting on day three of the cycle
  - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to oral lomustine.

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

References
1. British Neuro-oncology Society / pdfNCAt Rare Tumour Guidelines (June 2011). Accessed on 23/04/15 at http://www.bnos.org.uk/documents/rare_tumours_guidelines/Adult%20PNET%20guidelines.pdf
2. Packer RJ, Gajjar A, Vezina G et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average risk medulloblastoma. J Clin Oncol 2006; 25: 4202-4208.

REGIMEN SUMMARY

CISPLATIN-LOMUSTINE-VINCRISTINE (Packer LCV3)

Day 1

1. Aprepitant 125mg oral

2. Dexamethasone 4mg oral or intravenous
   Administration Instructions
   Omit this dose if the patient is already taking dexamethasone

3. Ondansetron 8mg oral or intravenous

4. Vincristine 1.5mg/m^2 (maximum 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

5. Furosemide 40mg oral or intravenous

6. 1000ml sodium chloride 0.9% intravenous infusion with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

7. Cisplatin 70mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 120 minutes)

8. 1000ml sodium chloride 0.9% intravenous infusion with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Day 8 and 15

9. Metoclopramide 10mg oral or intravenous

10. Vincristine 1.5mg/m^2 (maximum 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

Take Home Medicines (day 1)

1. Lomustine 75mg/m^2 once a day for one day on day 1 of the cycle oral
   Administration Instructions
   Swallow whole with a full glass of water. Do not open or chew

2. Aprepitant 80mg once a day for two days starting on day 2 of the cycle oral

3. Dexamethasone 4mg once a day for three days starting on day 2 of the cycle oral

4. Metoclopramide 10mg three times a day for three days then 10mg three times a day when required for the relief of nausea and vomiting oral

5. Ondansetron 8mg twice a day for three days starting on the evening of day 1 of the cycle oral

6. Ciprofloxacin 500mg twice a day for seven days starting on day 5 of the cycle oral

7. Growth factor according to local formulary choice. For example;

   - filgrastim or bioequivalent 30million units once a day subcutaneous for seven days starting on day three of the cycle
   - lenograstim or bioequivalent 33.6million units once a day subcutaneous for seven days starting on day three of the cycle
   - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two of the cycle

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Apr 2024	Update to include national dose banding. Remove OPCS codes	Donna Kimber Pharmacy Tech	Nanda Basker Pharmacist
1.1	Oct 2015	Dose of growth factors changed to million units from micrograms	Dr Deborah Wright Pharmacist	Dr Omar Al Salihi Consultant Clinical Oncologist
1	Oct 2015	None	Dr Deborah Wright Pharmacist	Dr Omar Al Salihi Consultant Clinical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Trust

All actions have been taken to ensure these protocols are correct. However, it remains the responsibility of the prescriber to ensure the correct drugs and doses are prescribed for patients.