Systemic Anti Cancer Therapy Protocol

PCV (Procarbazine, Lomustine and Vincristine) Glioma

PROTOCOL REF: MPHAPCVCNS
(Version No: 1.0)

Approved for use in:

- Adjuvant treatment for lower-grade gliomas (grades II and III)
- Palliative treatment for:
  - Recurrent/progressive low-grade gliomas
  - High-grade gliomas previously treated with temozolomide
- ECOG PS 0-2

Dosage:

Drug	Dose	Route	Frequency
Procarbazine	**150mg***	Oral	Days 2 to 11 of a 42 day cycle
Lomustine (CCNU)	**160mg****	Oral	Day 1 only of a 42 day cycle
Vincristine	**1.4 mg/m^2 (max. 2mg)**	IV infusion	Day 1 only of a 42 day cycle

***** Procarbazine dose is given as 50mg three times a day

****** Lomustine dose can increase to 200mg if well tolerated and BSA >1.9m^2

Adjuvant – up to 6 cycles

Palliative – until progression/unacceptable toxicity

Administration (Counselling Points):

Procarbazine - available as a 50mg capsule and can be taken with or without food. Please refer to “Interactions” section for information about high tyramine-containing foods which should be avoided whilst on procarbazine (a diet patient information sheet should be provided to patients at pre-assessment).

Lomustine (CCNU) - available as a 40mg capsule and should be taken on an empty stomach with water at BEDTIME (to reduce nausea).

Emetogenic risk:

Mild/moderate emetogenicity.

Supportive treatments:

- Ondansetron 8mg pre-chemotherapy on day 1 (cycle 1 only)
- Ondansetron 8mg twice a day for 3 days
- Domperidone 10mg three times a day when required

Extravasation risk:

Vincristine – vesicant – "dilute and disperse" (warm compress)

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	**Procarbazine**	Contra-indicated if CrCl <10ml/min
	Lomustine	Reduce dose by 25% if CrCl 30-50ml/min. Not recommended if CrCl <30ml/min
	Vincristine	No dose adjustments are required

Hepatic	**Procarbazine**	Contra-indicated in severe hepatic impairment
	Lomustine	Not recommended in severe hepatic impairment
	Vincristine	Bilirubin >51 µmol/L – 50% of original dose

Interactions:

Anti-depressants, opioids and anti-emetics - Procarbazine is a weak monoamineoxidase inhibitor (MAOI) so concurrent use may increase the risk of Serotonin Syndrome.

Anti-epileptics – increased risk of hypersensitivity reaction when phenobarbital, phenytoin or carbamazepine are given with procarbazine.

Alcohol - consumption of alcohol whilst taking procarbazine may cause a disulfiram-like reaction (nausea, vomiting, flushing, dizziness, and headache).

High tyramine-containing foods – tyramine is released as proteins age and breakdown therefore is usually found in aged, fermented, pickled or smoked foods or in food that has not been stored correctly and has started to spoil. The reaction to eating these foods whilst on procarbazine can be relatively mild (facial flushing and rash) but can also be quite severe (sudden onset headache, neck stiffness, nausea and vomiting, sensitivity to light, sweating, chills, pounding heart). Symptoms of any reaction usually resolve within a few hours. Food that should be completely avoided includes mature or aged cheese, concentrated yeast or meat extracts (marmite, gravy or stock cubes) and broad-bean pods. Food that may be eaten but in moderation include over-ripe fruit, beer, wine, sour cream, yoghurt, cured meats, banana and soy sauce.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron**	**8mg**	**PO**	30 mins before chemotherapy
	VINCRISTINE	**1.4 mg/m^2 (max. 2mg)**	**IV**	Sodium Chloride 0.9% 50ml over 15 minutes
	LOMUSTINE (CCNU)	**160mg***	**PO**	At night for 1 dose only
2 to 11	**PROCARBAZINE**	**50mg**	**PO**	Three times a day for 10 days

***** Lomustine dose can increase to 200mg if well tolerated and BSA >1.9m^2

Main toxicities:

Nausea and vomiting, anaemia, thrombocytopenia, neutropenia, lethargy

Procarbazine
Allergic skin reactions, loss of appetite , pneumonitis, abnormal LFT results
Lomustine (CCNU)
Disorientation, mucositis, pulmonary fibrosis, alopecia, renal injury/failure, increased bilirubin, increased transaminases
Vincristine
Neuropathy, constipation, arthralgia, myalgia, polyuria, dysuria, urinary retention, hypertension, hypotension

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X		X	X	Every cycle
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle
MRI scan	X			X	Every 3 months
Full Set of Observations (Blood pressure, respiratory rate, oxygen saturation, pulse)	X				Repeat if clinically indicated
Height recorded	X				
Weight recorded	X	X	X	X	Every cycle
Blood glucose	X				Repeat if clinically indicated

Dose Modifications and Toxicity Management:

If a dose reduction is indicated, PCV dose intensity is reduced as follows:

Dose Reduction	Advice
1st	Reduce duration of procarbazine from 10 day to 7 days
2nd	Reduce Lomustine (CCNU) dose to 120mg
3rd	Stop Procarbazine
4th	Reduce Lomustine (CCNU) dose to 80mg

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.5 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 1.4 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Neurotoxicity	
< Grade 1 or grade 2 persisting < 7 days	Continue vincristine at full dose
Grade 2 persisting > 7 days	Discontinue vincristine
Constipation / Ileus	
Ileus ≥ grade 2 lasting ≤ 7 days	Omit vincristine from next cycle. Discuss with consultant whether to re-start
Ileus ≥ grade 2 lasting > 7 days	Discontinue vincristine
Skin rash	
Grade 1 to 2	Suspend Procarbazine and omit for rest of cycle. Symptomatic treatment (antihistamine +/- topical creams). Prophylactic antihistamine with subsequent cycles.
Grade 3	Stop procarbazine

References:

1. https://www.medicines.org.uk/emc
2. BNF available via: https://bnf.nice.org.uk/
3. 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
4. NICE: CG99 Brain tumours (primary) and brain metastases in adults. Published date: July 2018