SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

PCV (Procarbazine, Lomustine and Vincristine) **CNS – Glioma**

PROTOCOL REF: MPHAPCVCNS
(Version No. 1.1)

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	**1.4mg/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 >1.9m2

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:

Moderately emetogenic.

Supportive treatments:

- Ondansetron 8mg Tablet – One hour before chemotherapy
- Cyclizine 50mg Tablets – 50mg up to 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**	Contraindicated 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**	Contraindicated in severe hepatic impairment
	Lomustine	Not recommended in severe hepatic impairment
	Vincristine	Bilirubin >51 µmol/L- 50% of original dose

Interactions:

Procarbazine:

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

Vincristine:

<u>Concomitant use contraindicated</u>

Yellow fever vaccine: risk of generalized disease mortal.

<u>Concomitant use not recommended</u>

- **Live attenuated vaccines** (except yellow fever): Risk of systemic, possible fatal disease. This is increased in subjects who are already immunosuppressed by their underlying disease. Use inactivated vaccine where this exist (poliomyelitis).
- **Phenytoin, fosphenytoin**: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration

- **Ciclosporin** (and by extrapolation **tacrolimus** and **sirolimus**): Excessive immunosuppression with risk of lymphoproliferation.
- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as **amino glycosides, vancomycin, capreomycin and diuretics**, may increase or exacerbate toxicity.0
- **Loop diuretics (furosemide,indapamide,bumetanide)**: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.
- Caution should be exercised in patients concurrently taking drugs known to inhibit/induce drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vincristine sulfate with **itraconazole** or **fluconazole** (known inhibitor of the metabolic pathway) have been reported to cause an earlier onset and/or an increased severity of neuromuscular side-effects, inducers like **St. John's wort** should be given cautiously. This interaction is presumed to be related to inhibition of the metabolism of vincristine.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron**	8mg	PO	30 min before chemotherapy
	Vincristine	1.4mg/m^2 (Max. 2mg)	IV	Sodium chloride 0.9% 50mL over 15 minutes
	Lomustine (CCNU)	160mg*	PO	At night on Day 1 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:

Lomustine		
System Organ Class	Frequency	
Blood and lymphatic system disorders	Very common	Leukopenia
	Not known	Bone marrow failure, thrombocytopenia, anaemia
Nervous system disorders	Not known	Coordination abnormal, disorientation, lethargy, dysarthria
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary fibrosis, lung infiltration
Gastrointestinal disorders	Not known	Nausea, vomiting, stomatitis
Hepatobiliary disorders	Not known	Transaminases increased, blood bilirubin increased
Skin and subcutaneous tissue disorders	Not known	Alopecia
Renal and urinary disorders	Not known	Renal failure, azotaemia, renal atrophy, renal injury

Procarbazine		
System Organ Class	Frequency	
Infections and infestations	Not known	Infections
Blood and lymphatic system disorders	Not known	Leucopenia Thrombocytopenia Neutropenia
Immune system disorders	Not known	Severe hypersensitivity reactions with angioedema, urticaria and a precipitous drop in serum complement
Psychiatric disorders	Not known	Lethargy
Respiratory, thoracic and mediastinal disorders	Not known	Pneumonitis
Ear and labyrinth disorders	Common	Deafness, vertigo, tinnitus, earache
Gastrointestinal disorders	Very common	Loss of appetite, nausea, vomiting
Hepatobiliary disorders	Not known	Hepatic complications

		including jaundice and abnormal liver function tests
Skin and subcutaneous tissue disorders	Not known	Allergic skin reactions
Reproductive system and breast disorders	Not known	Azoospermia, ovarian failure

Vincristine		
Gastrointestinal	Not known	Constipation, abdominal cramps, paralytic ileus, diarrhoea, nausea, vomiting, oral ulceration
General disorders	Not known	Arthralgia, myalgia
Urology	Not known	Polyuria, dysuria, urinary retention
Vascular disorders	Not known	Hypertension and hypotension have occured
Haematological	Common	Leukopenia, anaemia, haemolytic anaemia and thrombocytopenia
Nervous system	Common and cumulative	Neuropathy
Skin and subcutaneous tissue disorders	Common	Alopecia

Listed above are the most common toxicities. For a comprehensive list of potential toxicities please refer to the SPC:

Lomustine "medac" 40 mg - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) ,
Vincristine Sulphate 1 mg/ml Injection - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) ,
Procarbazine Capsules 50mg - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x	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				As appropriate
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 days 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	Plts ≥ 100 x 10^9 /L

Delay 1 week on day 1 if:

ANC < 1.5 x 10^9 /L	Plts < 100 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. The British National Formulary (BNF). Available at https://bnf.nice.org.uk
2. Lomustine 40mg Capsules Summary of Product Characteristics Available at: https://www.medicines.org.uk/emc/product/1401 Last updated Nov 2020.
3. Procarbazine 50mg Capsules Summary of Product Characteristics Available at: Procarbazine Capsules 50mg - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Last updated Dec 2014
4. Vincristine Sulphate 1mg/mL Injection Summary of Product Characteristics Available at: Vincristine Sulphate 1 mg/ml Injection - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
5. 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

Circulation/Dissemination

Date added into Q-Pulse	7th September 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
As of 5th April 2023	V 1.1	**Hugh O'Neill**	Updated to new protocol format Vincristine Interactions added Main toxicities updated to new format