PCV - Procarbazine, Lomustine and Vincristine (CNS)

Indication
Palliative therapy for advanced/recurrent glioma.
Adjuvant treatment for patients with co-deleted anaplastic tumours.

ICD-10 codes
Codes prefixed with C71.

Regimen details

Day	Drug	Dose	Route
1	Vincristine	1.5mg/m^2 (max. 2mg)	IV infusion
1	Lomustine	100mg/m^2	PO
1 to 10	Procarbazine	100mg/m^2	PO

Cycle frequency
42 days

Number of cycles
6 cycles

Administration
Vincristine is administered as an intravenous infusion in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. The nurse should remain with patient throughout infusion.

Lomustine is available as 40mg capsules. Lomustine capsules should be swallowed whole with water.

Procarbazine is available as 50mg capsules. Procarbazine should be swallowed whole with water.

Pre-medication
5HT$_3$-antagonist before lomustine on day 1 and BD on day 2.

Emetogenicity
This regimen has moderate emetogenic potential (with high emetogenic potential on days 1 and 2 due to lomustine).

Additional supportive medication
Mouthwash as per local policy
Laxatives as required.

Extravasation
Vincristine is a vesicant (Group 5).

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days

Investigations –pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFT	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	< 1.5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L **or** platelets < 100 x 10^9/L delay one week or until recovery and consider 75% dose of lomustine and procarbazine.

If platelets < 50 x 10^9/L delay one week or until recovery and consider reducing lomustine and procarbazine to 60% dose.

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) delay one week or until FBC recovers and consider reducing lomustine and procarbazine to 75% dose.

- **Renal impairment**

CrCl (mL/min)	**Lomustine dose**	**Procarbazine dose**	**Vincristine dose**
>60	100%	100%	100%
45-60	75%	100%	100%
30-44	50%	Consider 50% dose reduction	100%
<30	Discontinue	Discontinue	Discontinue

- **Hepatic impairment**

AST/ALT (x ULN)		**Bilirubin (x ULN)**	**Lomustine dose**	**Procarbazine dose**	**Vincristine dose**
<1.5	***and***	≤ 1.5	100%	100%	100%
1.5 -3	***and***	≤ 1.5	100%	50%	50%
3 - 5	***or***	1.5 - 3	50%	50%	50%
<5	***and***	3 - 5	50%	50%	Omit
>5	***or***	>5	Omit	Omit	Omit

- **Other toxicities**

Toxicity	**Definition**	**Dose adjustment**
Neuropathy	Grade 2 (moderate symptoms)	Reduce procarbazine to 75% dose Reduce vincristine to 67% dose
	Grade 3+ (severe symptoms, limiting self-care)	Discontinue treatment

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Pneumonitis / pulmonary fibrosis
Thromboembolism
Nephrotoxicity
Hypersensitivity and allergic reactions
Secondary malignancy
Bowel perforation
Pancreatitis
Myocardial infarction
SIADH
Teratogenicity
Infertility

- **Frequently occurring side effects**

Nausea or vomiting
Fatigue, flu-like symptoms
Anorexia, weight loss
Constipation, diarrhoea
Neurotoxicity
Myelosuppression
Stomatitis/mucositis

- **Other side effects**

Rash, pigmentation, photosensitivity
CNS depression, nightmares, hallucinations, insomnia

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin-derived anticoagulants such as warfarin: patients established on warfarin should either be changed to low molecular weight heparin or have weekly monitoring of INR. Patients who are initiated on anti-coagulation should remain on low molecular weight heparin until completion of the course of chemotherapy.
Phenytoin and fosphenytoin: close monitoring and/or alternative agents are recommended if co-prescribed with this regimen. Phenytoin serum levels may be decreased, possibly as a result of decreased absorption and/or increased metabolism.
Alcohol: Procarbazine has a weak disulfiram-like effect and can lead to alcohol intolerance.
MAO inhibition: Procarbazine is a weak inhibitor of MAO and can cause CNS side-effects. Care should be taken when co-prescribing antihypertensives, CNS depressants or tricyclic antidepressants.
Barbiturates: Phenobarbital can lead to a reduced anti-tumour effect of lomustine due to induction of hepatic enzymes and increased elimination. Barbiturates can cause increased CNS depression with procarbazine.
Fluconazole, itraconazole and posaconazole: increased risk of neuropathy, likely due to CYP3A4 inhibition. Avoid treatment 72 hours either side of vincristine dose if concurrent use cannot be avoided.

Additional comments

Haematological toxicity may be cumulative.
Lomustine can cause pulmonary problems after high, lifetime cumulative doses (>1,100mg/m^2). Onset of symptoms may occur months/years after treatment discontinued.

References

- Krens S D, Lassche, Jansman GFGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20:e201-08. Supplementary appendix
- Summary of Product Characteristics Lomustine (medac). Accessed 20 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics Procarbazine (medac). Accessed 20 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics Vincristine (Hospira). Accessed 20 September 2022 via www.medicines.org.uk
- Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. J Clin Oncol. 2001 Jan 15;19(2):509-18.

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