Procarbazine, Lomustine and vinCRIStine (PCV) Therapy – 56 days[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of Grade II glioma administered after radiotherapy	C71	00658a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Each cycle consists of:

- Lomustine orally on day 1
- Procarbazine orally on days 8 to 21
- vinCRIStine administered IV on days 8 and 29

repeated every 8 weeks (56 days) for 6 cycles or until disease progression or unacceptable toxicity develops.

PCV Therapy should start within 4 weeks after completion of radiotherapy.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	[a,b]Lomustine	110mg/m^2 ONCE a day	PO	N/A	Every 56 days for 6 cycles
8 to 21	[b,c]Procarbazine	60mg/m^2 ONCE a day	PO	N/A	Every 56 days for 6 cycles
8, 29	[d]vinCRIStine	1.4mg/m^2 (Dose capped at 2mg)	IV	50ml 0.9% NaCl over 10 min	Every 56 days for 6 cycles
[a]Lomustine is available as 40mg capsules.					
[b]Lomustine and procarbazine are unlicensed drugs. If the drug is not to be dispensed by the hospital, then the hospital should ensure communication with the patient's community pharmacy to ensure there is no interruption in treatment.					
[c]Procarbazine is available as 50mg capsules, round dose to nearest 50mg.					
[d]vinCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer. https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf					

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate renal and hepatic function

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EXCLUSIONS:

- Patients with hypersensitivity to procarbazine, lomustine, vinCRIStine or any of the listed excipients
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose

Regular tests:

- FBC, renal and liver profile prior to each treatment
- Pulmonary function tests if clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

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Haematological:

Table 1: Dose modifications* in haematological toxicity

	ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Treatment
Day 1 - Lomustine				
	≥1.0	and	≥ 100	Proceed if patient is well
	0.5 - 1.0	or	50 - 100	Delay and maintain dose of lomustine
	<0.5	or	<50	Delay and dose reduce lomustine by 25%
Day 8 - vinCRIStine and procarbazine				
	≥1.0	and	≥ 100	Proceed if patient is well
	0.5 - 1.0	or	50 - 100	Delay and maintain dose of vinCRIStine and procarbazine.
	<0.5	or	<50	Delay. Dose reduce procarbazine by 25%. Maintain dose of vinCRIStine
Day 29 – vinCRIStine				
	≥1.0	and	≥ 100	Proceed if patient is well
	0.5 - 1.0	or	50 - 100	Proceed if patient is well
	<0.5	or	<50	Omit dose
Preceding Cycle Nadir				
	< 0.5	or	<50	Reduce previous cycle's lomustine and procarbazine dose by 25%
***vinCRIStine dose will not be reduced for low treatment-day blood counts.**				

Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Lomustine	CrCl (ml/min)	Dose	Lack of information available. Consider dose reduction.			
	>60	100%				
	45-60	75%				
	30-45	50%				
	<30	Not recommended				
Procarbazine	**Serum creatinine**	**Dose**	**Bilirubin (micromol/L)**		**AST/ALT**	**Dose**
	> 177 micromol/L	50%	>50			Consider a dose reduction
	Severe renal impairment	Not recommended	>85	or	AST >180	Contra-indicated
vinCRIStine	No dose reduction necessary.		26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	> 180	Omit

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Management of adverse events:

Table 3: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Grade 3 or 4 neurotoxicity	Hold vinCRIStine. For severe abdominal or jaw pain, reduce vinCRIStine dose by 50% on all subsequent doses. Lomustine and procarbazine: Continue as per regimen.
Skin toxicity	Procarbazine: Interrupt and consider discontinuation if urticarial rash develops. Lomustine and vinCRIStine: Continue as per regimen.
Pulmonary toxicity	Lomustine: Hold if cough, shortness of breath, or other pulmonary symptoms develop and if the Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) is < 60% of predicted. Procarbazine and vinCRIStine: Continue as per regimen.
Nausea/vomiting (despite anti-emetics) and other toxicity: **Grade 3:** **Grade 4:**	 Reduce doses by 25% Reduce doses by 50%

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Lomustine	Day 1 Moderate to High	**(Refer to local policy)**
Procarbazine	Day 8-22 Moderate to High	**(Refer to local policy)**
vinCRIStine	Day 8 and 29 Minimal	**(Refer to local policy)**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Prophylactic regimen against vinCRIStine-induced constipation is recommended **(Refer to local policy)**.
- Lomustine can cause birth defects. Men and women are recommended to take contraceptive precautions during therapy with lomustine and for 6 months after treatment.

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Pulmonary toxicity:** Lomustine should be administered with caution in patients with a baseline below 70% of predicted forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO). Baseline pulmonary function studies should be carried out and repeated as clinically indicated during treatment. Pulmonary toxicity associated with lomustine appears to be dose-related.
- **Peripheral neuropathy:** vinCRIStine may cause peripheral neuropathy which is dose-related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months.
- **Extravasation:** vinCRIStine causes pain and possible tissue necrosis if extravasated **(Refer to local policy).**

DRUG INTERACTIONS:

- Procarbazine is a weak MAO inhibitor and therefore interactions with certain foodstuffs and drugs, although very rare, must be borne in mind. Thus, owing to possible potentiation of the effect of barbiturates, narcotic analgesics (especially pethidine), drugs with anticholinergic effects (including phenothiazine derivatives and tricyclic antidepressants), other central nervous system depressants (including anaesthetic agents) and anti-hypertensive agents, these drugs should be given concurrently with caution and in low doses.
- Intolerance to alcohol (Disulfiram-like reaction) may occur with procarbazine.
- Concurrent administration of vinCRIStine with allopurinol, pyridoxine or isoniazid may increase the incidence of cytotoxic induced bone marrow depression.
- CYP 3A4 enzyme inducers may increase the clearance of vinCRIStine.
- CYP 3A4 enzyme inhibitors may decrease the clearance of vinCRIStine.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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3. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.

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Version	Date	Amendment	Approved By
1	20/08/2021		Prof Patrick G Morris
2	23/06/2022	Amendment made to Table 1: Dose modifications in haematological toxicity.	Prof Patrick G Morris

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

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