PCV (Procarbazine + CCNU + Vincristine)
High Grade Gliomas

Background: The combination of Procarbazine, Lomustine (CCNU) and vincristine (PCV) is a treatment option for the adjuvant treatment of anaplastic astrocytoma, oligodendrogliomas and oligoastrocytomas, or for grade IV tumours not eligible for treatment with concurrent temozolomide and radiotherapy. It can also be used to treat recurrent high grade gliomas.

Patient Group: Adjuvant treatment for Grade III Gliomas (anaplastic astrocytoma, oligodendrogliomas and oligoastrocytomas).
First line treatment for grade IV tumours not eligible for concurrent chemoradiation regimen.
Recurrent high grade gliomas.
ECOG PS 0 – 2

Regimen Details

Vincristine 2mg  IV  day 1
(Maximum dose 2mg)
In 50mL IV infusion bag sodium chloride 0.9% administered over 5 – 10 minutes.

Lomustine 160mg  (BSA <1.9m²)  PO  day 1
200mg  (BSA > 1.9m²)  PO  day 1
(available as 40mg capsules)

Procarbazine 150mg  (BSA <1.9m²)  PO  days 1 – 10
200mg  (BSA >1.9m²)  PO  days 1 – 10
(available as 50mg capsules)

Repeated every 6 weeks for 6 cycles or until tumour progression.

NB Local decisions on flat dosing and dose capping are modifications of the MRC regimen (3) which itself is a modification of the original PCV regimen (5).

Pre-treatment assessment:
Weight, FBC, U&E’s, LFT’s and creatinine clearance (>60mL/min)
MRI Scan and histology

General haematological limits for inclusion:
Platelets > 100 x 10⁹/L
ANC > 1.5 x 10⁹/L
WBC ≥ 3 x 10⁹/L
Administration:
- Lomustine and procarbazine capsules must be swallowed whole with a glass of water and must not be opened or chewed.
- Vincristine is for intravenous infusion only and can be fatal if given by any other route. It should be labelled:
  “For INTRAVENOUS use only.
  FATAL if given by other routes.”
- Vincristine is a vesicant and care must be taken to avoid extravasation. The nurse administering the infusion MUST stay with patient during the infusion.
- The cannula must be checked for patency, back flow of blood witnessed before administration and any supporting bandage removed. This ensures that the cannula is well sited and the risk of extravasation minimized. If in any doubt about the integrity of cannula – RECANNUlate.
- Before administering vincristine, run a 50mL sodium chloride 0.9% infusion freely through the cannula, administer vincristine then flush with 50mL sodium chloride 0.9% before administering further chemotherapy agents.
- Ensure the patient keeps their arm still and informs the nurse of any discomfort during this administration.
- If any signs of extravasation occur follow the Extravasation Policy.

Anti-emetics: Highly emetogenic on day 1. Moderate to low emetogenicity on days 2 to 10. For those patients on long-term oral dexamethasone for their brain tumour, they will not need anti-emetic doses (IV or oral) of dexamethasone.

Additional Medication:
- Consider PCP prophylaxis with co-trimoxazole 960mg orally daily on Monday/ Wednesday/ Fridays.
- Patients may require treatment for focal seizures (lamotrigine or levetiracetam)

Monitoring and Assessment:
FBC and clinical examination – prior to each cycle of chemotherapy
- Platelets > 100 x 10^9/L
- ANC > 1.5 x 10^9/L
- WBC ≥ 3 x 10^9/L
U&E, LFTs - prior to each cycle of chemotherapy
MRI Scan - after cycle 2-3 to assess response and as clinically indicated.
Dose Modifications:

Haematological Toxicity
Treat at Full dose if WCC ≥ 3 x 10^9/L, ANC ≥ 1.5 x 10^9/L and platelet count ≥ 100 x 10^9/L. If thrombocytopenia or neutropenia, delay therapy until counts recovered. If > 1 delay in treatment due to neutropenia or thrombocytopenia, reduce procarbazine duration from 10 days to 7 days.
The haematological toxicity of lomustine may be cumulative, leading to successively lower white cell and platelet counts with successive doses of the drug.

Non-haematological Toxicity
If the patient develops a rash, they should stop procarbazine immediately. Procarbazine should then be omitted from future cycles.

Hepatic Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procarbazine</td>
<td>&gt;50</td>
<td>And normal</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&gt;85</td>
<td>Or &gt;180</td>
<td>omit</td>
</tr>
<tr>
<td>Vincristine</td>
<td>26-51</td>
<td>Or 60-180</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&gt;51</td>
<td>And normal</td>
<td>50%</td>
</tr>
<tr>
<td>Lomustine</td>
<td>&gt;25</td>
<td>&gt; 5 x ULN</td>
<td>omit or dose reduce</td>
</tr>
</tbody>
</table>

Renal Impairment

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Lomustine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
</tr>
<tr>
<td>45 – 60</td>
<td>Give 75%</td>
</tr>
<tr>
<td>30 - 45</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

For procarbazine, if serum creatinine > 177µmol/L, give 50% dose, and not recommended with severe renal failure (creatinine clearance < 10mL/min).

Pharmaceutical Care:
- Procarbazine is a weak MAO inhibitor and therefore certain foodstuffs should be avoided. These foods include: mature cheeses (including processed cheese and cream cheese are safe), yeast or meat extracts (Marmite, Oxo, Bovril), broad bean pods, pickled herring, salami sausage, flavoured textured vegetable protein, over-ripe fruit, alcoholic drinks (especially heavy red wines such as Chianti), non-
alcoholic beers, lagers and wines, other foods that are not fresh, particularly if they have been fermented, pickled, smoked, “hung” (game), or “matured”, miso soup and large amounts of soy sauce.

- Patients receiving warfarin (or other coumarin-derived anticoagulants) should have their INR monitored weekly or consider changing to a LMWH until chemotherapy is completed.
- **Avoid alcohol.** A disulfiram-like reaction may occur with procarbazine.

- The following drugs should be used with caution and in low doses with procarbazine: 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 agent.

- Phenytoin and fosphenytoin levels may be reduced and levels should be monitored and dose adjusted if necessary.

- Concomitant use of clozapine may increase the risk of agranulocytosis. Use with enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions to procarbazine.

- Lomustine in combination with theophylline or with the H₂-receptor antagonist cimetidine may potentiate bone marrow toxicity.

- Pre-treatment with phenobarbital can lead to a reduced anti-tumour effect of lomustine due to an accelerated elimination caused by induction of microsomal liver enzymes.

**Most Common Toxicities:**
- Myelosuppression +/- infection and bleeding
- Nausea and vomiting
- CNS depression, nightmares, insomnia, hallucinations
- Rash, pigmentation, radiation recall, photosensitivity
- Diarrhoea and stomatitis, anorexia
- Neurotoxicity – peripheral neuropathy
- Constipation, cramps (may be severe)
- Fatigue, flu like symptoms
- Taste changes
- Hair thinning

**Rare but serious side effects include:**
- Pneumonitis/pulmonary fibrosis (esp. if cumulative dose > 1100mg/m²)
- Nephrotoxicity
- Hypersensitivity reactions
- SIADH
References:

2. SPC Procarbazine Alliance Pharmaceuticals www.medicines.org.uk [accessed 29th August 2012]