Lomustine-Temozolomide chemo-RT and Adjuvant chemo for GBM (CeTeG / NOA-09 regimen)

Indication

Glioblastoma with methylated MGMT promoter, post resection in patients aged 18-70yrs of performance status 0-1 only.

Regimen details

- Lomustine 100mg/m^2, Oral ONCE. Days 1
- Temozolomide 100mg/m^2, Oral once a day. Days 2 to 6
- Radiotherapy given concurrently (for 6 weeks) starting with cycle 1 day 1 chemo.
- Aim for total 6 cycles of chemotherapy.

Cycle frequency

Repeat chemotherapy every 6 weeks / 42 days

Number of cycles

6 cycles. Concomitant radiotherapy with cycle 1 only.

Administration

- Temozolomide treatment should ideally be taken between 1 – 2 hours prior to radiotherapy, at the same time each day. Temozolomide capsules should be administered in the fasting state i.e. 1 hour before or 2 hours after food. The capsules are swallowed whole with a glass of water and must not be opened or chewed. If vomiting occurs after the dose is administered, a second dose should not be administered that day. Temozolomide hard capsules are available as 5mg, 20mg, 100mg, 140mg, 180mg, and 250mg capsules.
- Lomustine swallowed whole with water. Only available as 40mg capsules.

Pre-medication

Ondansetron 8mg PO Take BD for 6 days. Take the first dose 30 minutes before taking the Lomustine capsules.

Emetogenicity

This regimen has high emetogenic potential on days 1 and 2 due to lomustine.

Additional supportive medication

PCP prophylaxis: All patients should receive Co-trimoxazole 960mg on alternate days for 6 weeks
Metoclopramide 10mg po TDS prn or Cyclizine 50mg po TDS prn (if there is risk of seizure)

Investigations – pre first cycle

Standard network pre-SACT tests

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST) to be checked on day 20-25 and day 40-42.

Standard limits for administration to go ahead

CNS Table 3 Temozolomide + Lomustine + Radiotherapy Ref 1 & 2					
Haematology			**Temozolomide + Lomustine Dose Modifications**		
Haematology **Note:** Published reference gives dose reduction based solely on **White blood cell count** (WBC), not neutrophils (ANC), on day 25 and day 42 of each cycle. Drug dose adjustment is based on early (temozolomide) or late (lomustine) toxicity, using day 25 as the cut off for early or late.					
WBC x10^9/L		**ANC*** x10^9/L		Platelets x10^9/L	* Absolute neutrophil count
Day 40-42 to determine if next cycle can go ahead and lomustine dose					
≥ 3.0	and	≥ 1.5	and	≥ 100	If day 40-42 FBC above these levels treat on time with Lomustine: Continue with previous dose Temozolomide: Dose on time with dose adjusted based on nadir counts from day 25 below
1.5 - 2.9	or	1.0-1.5	Or	50 -99	Delay until recovered to above these levels then treat with Lomustine: Continue with previous dose Temozolomide: Dose on time with dose adjusted based on nadir counts from day 25 below
< 1.5	or	< 1.0	Or	< 50	Delay until recovered to above these levels then treat with Lomustine: Reduced by one dose level Temozolomide: Dose on time with dose adjusted based on nadir counts from day 25 below
WBC x10^9/L		Platelets x10^9/L			
Day 20- 25 : Nadir count to determine temozolomide dose for next cycle above					
> 2.5	or	> 100	Only treat if FBC on Day 42above permits and give Lomustine: Dose based on Day 42 count advice above Temozolomide: If radiotherapy is complete **and** counts are above these levels **and** the patient has not had any ≥ Grade 3 non-haematological toxicity : Temozolomide may be increased by ONE dose level Ref 2 Any Grade 3 non-hematologic toxicity at any time excludes dose escalation		
1.5 – 2.5	or	50-100	Only treat if FBC on Day 42above permits and give Lomustine: Dose based on Day 42 count advice above Temozolomide: Temozolomide same dose as previous cycle		
< 1.5	or	< 50	Only treat if FBC on Day 42 above permit and give Lomustine: Dose based on Day 42 count advice above Temozolomide: Reduce dose by ONE dose level		
< 1.0	or	< 25	Only treat if FBC on Day 42 above permit and give Lomustine: Dose based on Day 42 count advice above Temozolomide: Reduce dose by TWO dose levels		

Dose modifications

Dose Level Tables Lomustine and Temozolomide

Lomustine Dose Level Table	
Dose Levels	**Lomustine Dose (Ref1)**
Starting dose	100mg/m^2
Dose Level - 1	75mg/m^2
Dose Level - 2	50mg/m^2
Dose Level - 3	Permanently discontinue Lomustine

Lomustine

The principal adverse effect is marrow toxicity of a delayed or prolonged nature. It usually occurs four to six weeks after administration of the medicinal product and is dose-related

Thrombocytopenia appears about four weeks after a dose of Lomustine and lasts one or two weeks at a level around 80 – 100 x10^9/L.

Leucopenia appears after five to six weeks and persists for one or two weeks at about 4 – 5 10^9/L.

Temozolomide Dose Level Table		
Dose Levels	**Temozolomide Dose Reduction Ref 1**	**Temozolomide Dose Escalation Ref 1**
Dose Level + 3		200mg/m^2/day for 5 days
Dose Level + 2		150mg/m^2/day for 5 days
Dose Level + 1		120mg/m^2/day for 5 days
Starting dose	**100mg/m^2/day for 5 days**	
Dose Level - 1	75mg/m^2/day for 5 days	
Dose Level - 2	50mg/m^2/day for 5 days	
Dose Level - 3	Discontinue Temozolomide	

Temozolomide

(single agent temozolomide) myelosuppression was predictable (usually within the first few cycles, with the nadir between day 21 and day 28), and recovery was rapid, usually within 1-2 weeks. No evidence of cumulative myelosuppression was observed. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

Renal Impairment	Temozolomide + Lomustine Dose Modifications
Renal Impairment UCH 2009	
CrCl > 60ml/min	Lomustine: Full dose lomustine Temozolomide: Full dose temozolomide
45-60 mls/min	Lomustine: 75% dose lomustine Temozolomide: Full dose temozolomide

30 -45 mls/min	Lomustine: 50% dose lomustine Temozolomide: Full dose temozolomide
< 30mls/min	Lomustine: Not recommended Temozolomide: Discuss with consultant. SPC states: No data are available on the administration of temozolomide in patients with renal impairment. It is unlikely that dose reductions are required in patients with any degree of renal impairment. However, caution should be exercised when temozolomide is administered in these patients.

Hepatic Impairment	**Temozolomide + Lomustine Dose Modifications**
Hepatic Impairment	
Temozolomide	
Mild or moderate hepatic Impairment	**Temozolomide** SPC states: The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment. No dose reduction
Severe hepatic Impairment	Discuss with consultant: **Temozolomide** SPC states: No data are available on temozolomide in patients with severe hepatic impairment (Child's Class C). It is unlikely that dose reductions are required in patients with severe hepatic impairment. However, caution should be exercised when temozolomide is administered in these patients. The SPC also states Hepatic injury, including fatal hepatic failure, has been reported in patients treated with Temozolomide. If baseline LFTs are abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients with significant liver function abnormalities during treatment, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide
Lomustine	No data in SPC. If Bilirubin> ULN and/or ALT/AST > ULN discuss with consultant to consider dose reduction. BCCA advise hold lomustine if ALT/AST > 5xULN and Bilirubin > 20micromol/L until liver function returns to normal

Non Haematological toxicity except nausea, vomiting, alopecia	**Temozolomide + Lomustine Dose Modifications**
Non Haematological toxicity except nausea, vomiting, alopecia	
Grade ≤ 2	Continue temozolomide
Grade 3	Interrupt until toxicity resolved to ≤ grade 1. Once recovered discuss with consultant to omit the drug expected to be causing the toxicity or to change the regimen
Grade 4	Discontinue regimen

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

- **Serious side effects**
  - Neutropenia (~ 15% grade 3 or above)
  - Thrombocytopenia (~ 30% grade 3 or above)
  - Thromboembolism
  - Pneumonitis / dyspnoea
  - Hypersensitivity and allergic reactions
  - Myopathy
  - Hepatic failure
  - Teratogenicity
  - **Infertility – discuss fertility issues**
  - Opportunistic infections, including PCP, Herpes simplex and oral candidiasis

- **Frequently occurring side effects**
  - Myelosuppression (neutropenia, thrombocytopenia)
  - Nausea and vomiting
  - Fatigue
  - Anorexia, weight loss
  - Constipation or diarrhoea
  - Rash
  - Seizures, headache
  - Arthralgia/myalgia
  - Stomatitis/mucositis

- **Other side effects**
  - Drug induced hepatitis
  - Hearing impairment, tinnitus
  - Anxiety
  - Depression
  - Alopecia

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

For lomustine:

- 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.
- Barbiturates: Phenobarbital can lead to a reduced anti-tumour effect of lomustine due to induction of hepatic enzymes and increased elimination.

For temozolomide:

- Sodium valproate - may decrease clearance of temozolomide.

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

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THIS PROTOCOL HAS BEEN DIRECTED BY DR Lam, Tai Chung, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: July 2025
Review: July 2027
VERSION: 1