BC Cancer Protocol Summary for Therapy for Malignant Brain Tumours using Metronomic Dosing of Temozolomide

Protocol Code	*CNTEMOZMD*
Tumour Group	*Neuro-Oncology*
Contact Physician	*Dr. Rebecca Harrison*

ELIGIBILITY:

Patients must have:
- Recurrent malignant glioma, or
- Progression during or post-completion of CNAJTZRT protocol

Patients should have:
- WHO PS greater than or equal to 2
- Adequate renal and hepatic function

EXCLUSIONS:

Patients must not:
- Have received more than 6 cycles of adjuvant temozolomide in the past
- Be pregnant or breast feeding

CAUTION:

- Significant hematologic or other toxicity associated with temozolomide in the past
- Creatinine greater than 1.5X normal
- Significant hepatic dysfunction

TESTS:

- Baseline: CBC and differential, platelets, ALT and bilirubin, creatinine, glucose (patients on dexamethasone)
- Before each treatment:
  - Day 1: CBC and differential, platelets, ALT and bilirubin
  - Day 22: CBC and differential, platelets
- Every second (ie, odd-numbered) treatment cycle (BEFORE #1, 3, 5, etc): creatinine
- Neuroimaging: every 2 cycles
- If clinically indicated: electrolytes, magnesium, calcium, glucose

PREMEDICATIONS:

- ondansetron 8 mg given 30 minutes prior to first dose of temozolomide
- prochlorperazine 10 mg PO q6h prn or dimenhyDRINATE 25 to 50 mg PO q6h prn

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
temozolomide	50 mg/m^2 once daily x 28 days (days 1 to 28)	PO

*refer to Temozolomide Suggested Capsule Combination Table for dose rounding

- Repeat every 28 days to a maximum of 24 cycles.
- Discontinue for clinical or radiographic progression.

DOSE MODIFICATIONS:

1. **Hematological**

Day 1:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
greater than or equal to 1.5	and	greater than or equal to 100	100%
less than 1.5	or	less than 100	Delay x 1 week*

* Follow CBC weekly and re-institute temozolomide at 35 mg/m^2 if ANC recovers to greater than 1.5 x 10^9/L and platelets recover to greater than 100 x 10^9/L within 3 weeks

Day 22:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
greater than or equal to 1.0	and	greater than or equal to 50	100%
less than 1.0	or	less than 50	Reduce next cycle to 35 mg/m^2 once daily

- Note: Dose reductions below 35 mg/m^2 are not permitted. Temozolomide should be discontinued for repeat grade 3 or 4 hematologic toxicity (ANC less than 1 x 10^9/L, platelets less than 50 x 10^9/L) at the 35 mg/m^2 dose.

2. Renal dysfunction: Dose modification required for creatinine greater than 2 x upper limit of normal. Reduce to 35 mg/m² and discontinue if no resolution of renal dysfunction at this dose.

3. Hepatic Dysfunction

Bilirubin (micromol/L)		ALT	Dose
less than 25	or	less than or equal to 2.5 x ULN	100%
25 to 85	or	2.6 to 5 x ULN	35 mg/m^2
greater than 85	or	greater than 5 x ULN	Delay***

*** Follow LFTs weekly and re-institute temozolomide at 35 mg/m² if Bilirubin recovers to less than 85 micromol/L and ALT recovers to less than 5 x ULN

- Note: Dose reductions below 35 mg/m^2 are not permitted. Temozolomide should be discontinued for repeat Bilirubin greater than 85 micromol/L and repeat ALT greater than 5 x ULN

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Thrombocytopenia:** Day 22 platelet counts less than 50 x 10^9/L should be monitored at least twice weekly until recovering. Platelet counts less than 20 x 10^9/L and falling should be treated with platelet transfusion.

Call Dr. Rebecca Harrison or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Perry JR, Mason WP, Belanger K, et al. The temozolomide RESCUE study: A phase II trial of continuous (28/28) dose-intensive temozolomide (TMZ) after progression on conventional 5/28 day TMZ in patients with recurrent malignant gliomas (abstr). J Clin Oncol 2008;26(15S):91s.
2. Tolcher AW, Gerson SL, Denis L, et al. Marked inactivation of O6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules. Br J Cancer 2003;88(7):1004-11.
3. Neyns B, Chaskis C, Joosens E, et al. A multicenter cohort study of dose-dense temozolomide (21 of 28 days) for the treatment of recurrent anaplastic astrocytoma or oligoastrocytoma. Cancer Invest 2008;26:269-77.
4. Yung WKA, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Brit J Cancer 2000;83:588-93.