BC Cancer Protocol Summary for Therapy for Recurrent Malignant Brain Tumours using Temozolomide and Etoposide

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

ELIGIBILITY:

Patients must have:

- Recurrent embryonal tumours such as medulloblastoma, or
- Recurrent gliomas in temozolomide naïve patients

Patients should have:

- Karnofsky Performance Status greater than 50
- Adequate bone marrow, cardiac, renal and hepatic function

EXCLUSIONS:

- Pregnant or breast feeding women

CAUTION:

- Significant hepatic dysfunction

TESTS:

- Baseline: CBC & Diff, ALT and total bilirubin, creatinine, glucose (patients on dexamethasone)
- Before each treatment:
  - Day 1: CBC & Diff, creatinine, ALT, total bilirubin, random glucose
  - Day 22: CBC & Diff
- Neuroimaging every 2 cycles
- If clinically indicated: electrolytes, magnesium, calcium

PREMEDICATIONS:

- ondansetron 8 mg given 30 minutes prior to each dose of temozolomide
- prochlorperazine 10 mg or metoclopramide 10-40 mg PO q4-6 hours prn with etoposide doses
- hydrocortisone and diphenhydrAMINE for history of hypersensitivity to etoposide

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
temozolomide	150 mg/m^2 once daily x 5 days (d 1-5)*	PO
etoposide	50 mg/m^2 once daily x 12 days (d 1-12)**	PO

* refer to Temozolomide Suggested Capsule Combination Table for dose rounding
** round dose to nearest 50 mg

Repeat every 28 days x 12 cycles

- Temozolomide dose may be increased to 200 mg/m^2 for the second cycle if no significant hematologic, hepatic or other toxicity is noted (see below)
- Discontinue for clinical or radiographic progression.

DOSE MODIFICATIONS:

1. Hematological

Day 1:

ANC (x10^9/L)		Platelets (x10^9/L)	Temozolomide Dose	Etoposide Dose
greater than or equal to 1.5	and	greater than or equal to 100	100%	100%
1.0 to 1.4	and	75 to 99	delay*	delay*
less than 1	and	less than 75	delay**	delay**

Dose levels for temozolomide are 200 mg/m^2, 150 mg/m^2 and 100 mg/m^2

** Follow CBC weekly and re-institute temozolomide at minus one dose level and etoposide at 50 mg/m^2 if ANC recovers to 1.5 x 10^9/L and platelets recover to 100 x 10^9/L within 3 weeks*

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

*For **repeat** grade 3 or 4 hematologic toxicity (ANC less than 1 x 10^9/L, platelets less than 50 x 10^9/L), discontinue etoposide and continue temozolomide at the 100 mg/m^2 dose.*

Day 22:

ANC (x10^9/L)		Platelets (x10^9/L)	Temozolomide dose	Etoposide dose
greater than or equal to 1.0	and	greater than or equal to 50	100%	100%
less than 1.0	or	less than 50	reduce one dose level	35 mg/m^2

Dose levels for temozolomide are 200 mg/m^2, 150 mg/m^2 and 100 mg/m^2

Note: Temozolomide dose reductions below 100 mg/m^2 are not permitted.

2. **Hepatic Dysfunction**

Bilirubin (micromol/L)		ALT	Temozolomide dose	Etoposide dose
less than 25	or	less than or equal to 2.5 x ULN	100%	100%
25 to 84	or	2.6 to 5 x ULN	reduce one dose level	35 mg/m^2
greater than 85		greater than 5 x ULN	delay*	delay*

Dose levels for temozolomide are 200 mg/m², 150 mg/m² and 100 mg/m²
*Follow LFTs weekly and re-institute temozolomide at 100 mg/m² and etoposide at 35 mg/m^2 if Bilirubin recovers to less than 85 micromol/L and ALT recovers to less than 5 x ULN
Note: Temozolomide dose reductions below 100 mg/m^2 are not permitted.
For **repeat** Bilirubin greater than 85 micromol/L and repeat ALT greater than 5 x ULN, discontinue both drugs

3. **Renal dysfunction**

Creatinine clearance (mL/min)	Temozolomide dose	Etoposide dose
Greater than 50	100%	100%
15 to 50*	100%	75%
Less than 15	Discontinue	Discontinue

*See precautions below.

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.
3. **Renal Dysfunction:** Renal impairment is not expected to affect temozolomide clearance. Caution should be exercised when treating patients with creatinine clearance less than 36 mL/min.

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. Korones NK, Smith A, Foreman N, Bouffet E. Temozolomide and oral vp-16 for children and young adults with recurrent or treatment-induced malignant gliomas. Pediatr Blood Cancer 2006;47:37-41.
2. Korones NK, Benita-Weiss M, Coyle TE et al. Phase I study of temozolomide and escalating doses of oral etoposide for adults with recurrent malignant glioma. Cancer 2003:97(8)1963-8.
3. Sandhu G, Adattini J, Armstrong Gordon E, O'Neill N. On behalf of the ADDIKD Guideline Working Group. International consensus guideline on anticancer drug dosing in kidney dysfunction. 2022. eviQ, Cancer Institute NSW. St Leonards, Australia.