

BCCA Protocol Summary for Palliative Therapy of Metastatic Neuroendocrine Cancer using Temozolomide and Capecitabine

Protocol Code *UGIAVTZCAP*

Tumour Group *Gastrointestinal*

Contact Physician *GI Systemic Therapy*

ELIGIBILITY:

- First or second line, metastatic, low to intermediate grade neuroendocrine tumours of the pancreas, in patients who are ineligible for GIENDO2
- ECOG performance status 0-1
- Adequate marrow reserve (ANC greater than or equal to $1.5 \times 10^9/L$, platelets greater than $100 \times 10^9/L$)
- Adequate renal function (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 35 micromol/L; AST/ Alkaline Phosphatase less than or equal to 5 x ULN)
- Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness
- Caution in patients with baseline more than 3 loose BM per day (in patients without colostomy or ileostomy)
- A BCCA “Compassionate Access Program” or “Undesignated Indication” request with appropriate clinical information for each patient must be approved prior to treatment

EXCLUSIONS:

- severe renal impairment (calculated creatinine clearance less than 30 mL/min, see Cockcroft-Gault equation under Dose Modifications)
- suspected Dihydropyrimidine Dehydrogenase (DPD) deficiency (see Precautions)
- severe hepatic dysfunction (total bilirubin greater than 50 micromol/L)

TESTS AND MONITORING:

- Baseline: CBC and differential, platelets, creatinine, liver function tests (Bilirubin, AST, Alkaline Phosphatase), appropriate imaging studies and tumour markers
- **Prior to** each cycle: CBC and differential, platelets, creatinine and liver function tests (Bilirubin, AST, Alkaline Phosphatase)
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR **prior to** each cycle.
- If clinically indicated: electrolytes, magnesium, calcium and glucose

PREMEDICATIONS:

- Antiemetic protocol for high moderate emetogenic chemotherapy (see SCNAUSEA)

TREATMENT:

Drug	Dose*	BCCA Administration Guideline
Capecitabine	750 mg/m ² BID x 14 days (d 1-14) (Total daily dose = 1500 mg/m ² /day)	PO with food
Temozolomide	200 mg/m ² daily x 5 days (d 10-14)	PO on an empty stomach (30-60 minutes before a meal or 2 hours after a meal)

Repeat every 28 days for a maximum of 12 cycles.

DOSE MODIFICATIONS:

1. Hematological:

- Dose modification is for both Capecitabine and Temozolomide

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th Event Dose
greater than or equal to 1.5	and	greater than or equal to 75	100%	100%	100%	100%
1 – 1.49	or	50-74.9	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
0.5-0.99	or	25-49.9	delay* then 75%	delay then 50%	discontinue	discontinue
less than 0.5	or	less than 25	discontinue or delay* then 50%	discontinue	discontinue	discontinue

*delay until ANC greater than or equal to 1.5 x 10⁹/L and platelets greater than or equal to 75 x 10⁹/L

- Platelet counts less than 50 x 10⁹/L should be monitored at least twice weekly until recovering. Platelet counts less than 20 x 10⁹/L and falling should be treated with platelet transfusion.

2. Hand-Foot Skin Reaction:

- if treatment is interrupted due to toxicity, retain the original stop and start dates (ie, do not make up for missed doses when treatment is resumed)

Grade	Hand-Foot Skin Reaction	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th Event Dose
1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	100%	100%	100%	100%
2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	delay* then 100%	delay* then 75% dose of Capecitabine	delay* then 50% dose of Capecitabine	discontinue
3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	delay* then 75% dose of Capecitabine	discontinue or delay* then 50% dose of Capecitabine	discontinue	discontinue

*stop treatment immediately and delay until resolved to grade 0-1

3. Other Non-Hematological Toxicity:

- see next table for toxicity grading criteria for diarrhea, nausea and vomiting, and stomatitis
- Dose modification for nausea and vomiting is for both Capecitabine and Temozolomide; dose modification for diarrhea or stomatitis is for Capecitabine only.
- if treatment is interrupted due to toxicity, retain the original stop and start dates (ie, do not make up for missed doses when treatment is resumed)

Toxicity Grade	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th Event Dose
0-1	100%	100%	100%	100%
2	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3 or 4	delay* then 50%	discontinue	discontinue	discontinue

*stop treatment immediately and delay until toxicity resolved to grade 0-1

Toxicity Criteria

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0-1	Increase of 2-3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4-6 stools/day or nocturnal stools	2-5 vomits/day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Increase of 7-9 stools/day or incontinence, malabsorption	6-10 vomits/day and cannot eat	Painful erythema, edema or ulcers and cannot eat
4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	10 vomits or more per day or requires parenteral support; dehydration	Mucosal necrosis, requires parenteral support

4. Hepatic dysfunction: Dose modification is required for elevations in transaminases greater than 5X upper limit of normal. Reduce Temozolomide dose to 100 mg/m². Discontinue treatment if no improvement in liver enzymes at that dosage. Capecitabine has not been studied in severe hepatic dysfunction.

5. Renal dysfunction:

Creatinine Clearance mL/min	Dose
greater than 50	100%
30-50	75% dose of Capecitabine
less than 30	0%

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance: (mL/min)} = \frac{N (140 - \text{age}) \text{ wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

$$N = 1.23 \text{ male}$$

$$N = 1.04 \text{ female}$$

PRECAUTIONS:

- 1. Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- 2. Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.

3. **Possible interactions with warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during capecitabine therapy and for 1 month after stopping capecitabine).
4. **Myocardial ischemia and angina** occurs rarely in patients receiving Capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment.

Call the GI Systemic Therapy physician at your regional cancer centre or Dr. Sanjay Rao at (250) 712-3900 or 1-888-563-7773 with any problems or questions regarding this treatment program.

Date activated: 01 Mar 2009

Date revised: 01 May 2011 (minor edit in Test Section)

References:

1. Fine RL, Fogelman DR and Schreiber SM. Effective treatment of Neuroendocrine Tumors with Temozolomide and Capecitabine. J Clin Oncol 2005; 23(June 1 Suppl):4216.
2. Isacoff WH, Moss RA, Pecora AL and Fine RL. Temozolomide/Capecitabine Therapy for Metastatic Neuroendocrine Tumors of the Pancreas. A Retrospective Review. J Clin Oncol 2006;24 (June 20 Suppl):14023.
3. Strosberg JR, Choi J, Gardner N and Kvolts L. First-line Treatment of Metastatic Pancreatic Endocrine Carcinomas with Capecitabine and Temozolomide. J Clin Oncol 2008; 26 (May 20 Suppl) abstr 4612.
4. Ekeblad S, et al. Temozolomide as Monotherapy is Effective in Treatment of Advanced Malignant Neuroendocrine Tumors. Clin Cancer Res. 2007 May 15;13(10):2986-91.