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

Protocol Code	*GIAVTZCAP*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

- First or second line, metastatic, low to intermediate grade neuroendocrine tumours of the pancreas
- ECOG performance status 0-1

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)

CAUTIONS:

- Adequate marrow reserve, renal and liver function
- Patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness
- Patients with baseline more than 3 loose BM per day (in patients without colostomy or ileostomy)

TESTS AND MONITORING:

- Baseline: CBC and differential, platelets, creatinine, liver function tests (Bilirubin, ALT), appropriate imaging studies. Optional : CgA, 24h urine 5-HIAA
- Prior to each cycle: CBC and differential, platelets, creatinine and liver function tests (Bilirubin, ALT)
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.
- If clinically indicated: electrolytes, magnesium, calcium, glucose, CgA, 24h urine 5-HIAA
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.

PREMEDICATIONS:

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

Activated: 1 Mar 2009 Revised: 1 Oct 2021 (ST chair and contact, eligibility, tests and monitoring updated. Moved cautions from Eligibility to separate heading “Cautions”, removed auxiliary information)

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
capecitabine	750 mg/m^2 BID x 14 days (d 1 to 14) (Total daily dose = 1500 mg/m^2/day)	PO
temozolomide	200 mg/m^2 daily x 5 days (d 10 to 14)	PO

*refer to Capecitabine Suggested Tablet Combination Table and Temozolomide Suggested Capsule Combination Table for dose rounding

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)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
greater than or equal to 1.5	and	greater than or equal to 75	100%	100%	100%	100%
1.0 to less than 1.5	or	50 to less than 75	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
0.5 to less than 1.0	or	25 to less than 50	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 10^9/L and platelets greater than or equal to 75 x 10^9/L

- 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.

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	1st Event Dose	2nd Event Dose	3rd Event Dose	4th 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	1st Event Dose	2nd Event Dose	3rd Event Dose	4th 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:

Bilirubin (micromol/L)		ALT	Temozolomide Dose
less than 25	or	less than or equal to 2.5 x ULN	200 mg/m^2
25 to 50	or	2.6 to 5 x ULN	100 mg/m^2
greater than 50	or	greater than 5 x ULN	Delay*

*Follow LFTs weekly and re-institute temozolomide at 100 mg/m^2 if bilirubin recovers to less than 50 micromol/L and ALT recover to less than 5 x ULN

Capecitabine has not been studied in severe hepatic dysfunction.

5. Renal dysfunction:

Creatinine Clearance mL/min	Dose
greater than 50	100%
30 to 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 male

N = 1.04 female

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
3. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). If patient is taking capecitabine, it should be stopped until given direction by the physician. Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
4. **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.
5. **Possible drug interaction with capecitabine and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during capecitabine therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of capecitabine, repeat INR weekly for one month.
6. **Possible drug interaction with capecitabine and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Capecitabine may increase the serum concentration of these two agents.

Call the GI Systemic Therapy physician at your regional cancer centre or Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Fine RL, Fogelman DR and Schreibman 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 Kvols 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.