BC Cancer Protocol Summary for Adjuvant Chemotherapy for Resected Pancreatic Adenocarcinoma using Capecitabine and Gemcitabine

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

ELIGIBILITY:
- Node negative or positive pancreatic adenocarcinoma
- Macroscopic complete resection (R0 or R1)
- ECOG performance status 0-2.

EXCLUSIONS:
- Severe renal impairment (calculated creatinine clearance less than 30 mL/min,
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Severe hepatic dysfunction (total bilirubin greater than 50 micromol/L).

CAUTIONS:
- Adequate marrow reserve and liver function
- Patients with recent MI, uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness

TESTS:
- Baseline: CBC and differential, platelets, LFTs (bilirubin, ALT, alkaline phosphatase), creatinine, sodium, potassium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine), appropriate imaging study. Optional: CA 19-9
- Prior to Day 1: CBC and differential, platelets, creatinine
- Prior to Day 8 and 15: CBC and differential, platelets
- If clinically indicated: BUN, sodium, potassium, LFTs (bilirubin, ALT, alkaline phosphatase)
- For patients on warfarin: Weekly INR during treatment
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.

PREMEDICATIONS:
Antiemetic protocol for low emetogenic chemotherapy. May not need any antiemetic with capecitabine. (see SCNAUSEA).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
gemcitabine	1000 mg/m^2 on days 1, 8, 15	IV in 250 mL NS over 30 minutes
capecitabine*	830 mg/m^2 PO BID on days 1 to 21 (Total daily dose = 1660 mg/m^2)	PO

* Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Repeat every 28 days x 6 cycles.

DOSE MODIFICATIONS:

Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

1. Hematology – On Treatment Day

ANC (x 10^9/L)		Platelets (x 10^9/L)	Gemcitabine Dose (Day 1, 8, 15)
greater than or equal to 1.0	and	greater than or equal to 100	100%
0.5 to less than 1.0	or	50 to less than 100	75%
less than 0.5	or	less than 50	Day 1: Delay Day 8,15: Omit

Doses of capecitabine generally do not require modifying for hematologic toxicity.

After 1 week delay, gemcitabine can be dosed according to ANC and platelet count.
After 2 or 3 week delay, gemcitabine should be reduced to 75% in all subsequent treatments even if ANC and platelet count recover completely.

Gemcitabine dose may be re-escalated after dose reduction if ANC and platelet count recover and if clinically appropriate. If after dose reduction, blood count is still inadequate, do not re-escalate dose.

Clinical Scenario	Gemcitabine Dose for Next Treatment	Capecitabine Dose for Next Treatment
Dose reduction for 1 week	Dose according to ANC and/or platelet count on day of treatment	Continue 100%
Dose reduction for 2 **consecutive** weeks	75% of full dose with no re-escalation	Continue 100%
Initial dose omission for 1 week	75% of full dose with no re-escalation	Continue 100%
Recurrent dose omission or delay greater than or equal to 2 weeks	75% of full dose with no re-escalation	75% of full dose with no re-escalation

2. Febrile Neutropenia
Following an episode of febrile neutropenia, all subsequent treatments should have the following dose adjustments for both gemcitabine and capecitabine:
Withhold until recovery then continue at 75% of the full dose with no re-escalation. If patient is already receiving 75% of the full dose, then a further dose reduction to 50% of the full dose should be made.

3. Hand-Foot Skin Reaction: capecitabine

- 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%	delay* then 50%	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%	discontinue or delay* then 50%	discontinue	discontinue

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

4. Other Non-Hematological Toxicities: capecitabine

See next table for toxicity grading criteria for diarrhea, nausea and vomiting, and stomatitis

- 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 to 1	100%	100%	100%	100%
2	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	delay* then 75%	delay* then 50%	discontinue	discontinue
4	discontinue or delay* then 50%	discontinue	discontinue	discontinue

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

Toxicity Criteria

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0-1	Increase of 2 to 3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4 to 6 stools/day or nocturnal stools	2 to 5 vomits/day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Increase of 7 to 9 stools/day or incontinence, malabsorption	6 to 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

5. Renal dysfunction:

Creatinine Clearance mL/min	capecitabine Dose	gemcitabine Dose
greater than 50	100%	100%
30 to 50	75%	100%
less than 30	discontinue	discontinue

Cockcroft-Gault Equation:

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

N = 1.23 male
N = 1.04 female

6. Hepatic dysfunction:

Dose modification may be required. Capecitabine has not been studied in severe hepatic dysfunction. Gemcitabine should be used with caution in patients with impaired liver function.

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. **Renal Dysfunction**: Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
5. **Pulmonary Toxicity**: Acute shortness of breath may occur with gemcitabine. Discontinue treatment if drug-induced pneumonitis is suspected.
6. **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.
7. **Possible drug interaction with warfarin and capecitabine and gemcitabine** has been reported and may occur at any time. Close monitoring is recommended. For patients on warfarin, weekly INR 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 treatment, repeat INR weekly for one month.
8. **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 the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1) Neoptolemos, JP et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicenter, open-label, randomized, phase 3 trial. Lancet 24Jan2017(online)
2) Cunningham, D et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009;27(33):5513-8.