

BCCA Protocol Summary for Adjuvant Therapy for Resected Pancreatic Cancer using Leucovorin and Fluorouracil

Protocol Code
Tumour Group
Contact Physician

GIPAJFF
Gastrointestinal
GI Systemic Therapy

ELIGIBILITY:

- Completely resected Stage I, II or III adenocarcinoma of the pancreas

TESTS:

- Baseline: CBC & diff, CEA, bilirubin, calculated creatinine clearance
- Before each treatment: CBC & diff
- If clinically indicated: bilirubin

PREMEDICATIONS:

- Treatment is non-emetogenic. See SCNAUSEA protocol.

TREATMENT:

See dose modifications for patients with significant co-morbid conditions.

Drug	Dose	BCCA Administration Guideline
Leucovorin (Folinic Acid)	20 mg/m ² /day x 5 days (d1-5)	IV push prior to Fluorouracil
Fluorouracil (5FU)	425 mg/m ² /day x 5 days (d1-5)	IV push

Repeat every 28 days X 6 cycles

Post-operative chemotherapy should preferably be started no later than 8 weeks after surgery.

If treatment cannot be given Monday to Friday, then the 5th dose should be given on the next available working day rather than giving the total dose over 4 days.

Some patients may experience stomatitis and/or diarrhea during Days 1-5 requiring dose modifications and/or treatment discontinuation due to excessive sensitivity. It is essential that all patients be assessed for stomatitis and diarrhea at each treatment visit and that any signs of these toxicities be reported to the attending physician or designate prior to administering the chemotherapy for that day. Continuing chemotherapy in this setting may result in life threatening toxicity.

DOSE MODIFICATIONS:

The dose of Leucovorin (Folinic Acid) is not modified for toxicity but is omitted if Fluorouracil is omitted

- For patients with significant co-morbid conditions (e.g. history of cardiac disease, stroke, COPD, insulin dependent diabetes), Performance Status 2 or more, or baseline creatinine clearance of ≤ 75 ml/min, start at:

Cycle 1: 375 mg/m²/day x 5 days (d1-5).

Cycle 2: 400 mg/m²/day x 5 days (d1-5) if no side effects at starting dose.

Cycles 3-6: 425 mg/m²/day x 5 days (d1-5) if no side effects after cycle 2.

Dose Levels for Toxicities

Agent	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Fluorouracil	425 mg/m ² or 100% of full dose	340 mg/m ² or 80% of full dose	300 mg/m ² or 70% of full dose	Discontinue Therapy

2. Hematologic Toxicity

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	ANC (x10 ⁹ /L)	Fluorouracil
<ul style="list-style-type: none"> ▪ If ANC < 1.5 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is ≥ 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). ▪ If ANC remains < 1.5 after 2 weeks, discontinue treatment. 	1	≥ 1.5	Maintain dose level
	2	1.0 – 1.49	Maintain dose level
	3	0.5 – 0.99	↓ 1 dose level
	4	< 0.5	↓ 1 dose level
	Grade 4 neutropenia and ≥ Grade 2 fever		↓ 2 dose levels

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	Platelets (x10 ⁹ /L)	Fluorouracil
<ul style="list-style-type: none"> ▪ If platelets < 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If platelets ≥ 75 within 2 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). ▪ If platelets remain < 75 after 2 weeks, discontinue treatment. 	1	≥ 75	Maintain dose level
	2	50 – 74.9	Maintain dose level
	3	10 – 49.9	↓ 1 dose level
	4	< 10.0	↓ 1 dose level

3. Non Hematologic Toxicity

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	Diarrhea	Fluorouracil
<ul style="list-style-type: none"> ▪ If diarrhea \geq Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea $<$ Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. ▪ If diarrhea remains \geq Grade 2 after 2 weeks, discontinue treatment. 	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	↓ 1 dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 2 dose levels
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 2 dose levels

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	Stomatitis	
<ul style="list-style-type: none"> ▪ If stomatitis \geq Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis $<$ Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. ▪ If stomatitis remains \geq Grade 2 after 2 weeks, discontinue treatment. 	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	↓ 1 dose level
	3	Painful erythema, edema, ulcers, and cannot eat	↓ 2 dose levels
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 2 dose levels

If multiple toxicities are seen, the dose administered is based on the most severe toxicity experienced. Viral infection, alopecia, fatigue, anorexia and nausea/vomiting controlled by antiemetics require no dose modification. All other non-hematologic toxicities are managed in the same manner as diarrhea. Dose reductions continue for remaining cycles.

4. Hepatic dysfunction: **Omit treatment if bilirubin >85 $\mu\text{mol/L}$ unless secondary to biliary obstruction (see BCCA Cancer Drug Manual).**

PRECAUTIONS:

1. **Diarrhea** with cramping occurs more commonly in previously radiated patients especially in the elderly. A GI syndrome characterized by progression from mild GI symptoms to potentially fatal enterocolitis has also been reported. Prompt attention, especially to ensure adequate hydration, is required.
2. **Neutropenia:** fever or other evidence of infection must be assessed promptly and treated aggressively; there is an increased risk of myelosuppression in elderly.
3. **Stomatitis:** Sucking ice chips (oral cryotherapy) is recommended, especially at higher doses of Fluorouracil, to reduce mucositis following chemotherapy. Remove dentures and place ice chips in mouth 5 minutes **before** chemotherapy. Continuously swish ice chips in mouth for 30 minutes, replenishing as ice melts. This may cause numbness or headaches, which subside quickly.
4. Dipyrimidine dehydrogenase deficiency may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity. This deficiency is thought to be severe in about 3% of the population.
5. Myocardial ischemia and angina occurs rarely in patients receiving Fluorouracil. 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. Hagen Kennecke at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 01 September 2004

Date revised: 01 March 2006 (contact physician)

Reference:

Neoptolemos JP et al A Randomized Trial of Chemoradiotherapy and Chemotherapy after Resection of Pancreatic Cancer, NEJM 2004;350:1200-10