BC Cancer Protocol Summary for First-Line Palliative Treatment of Metastatic Anal Squamous Cell Carcinoma using CARBOplatin and Weekly PACLitaxel

Protocol Code: *GIAAVCT*

Tumour Group: *Gastrointestinal*

Contact Physicians: *GI Systemic Therapy*

ELIGIBILITY:

Patients must have:
- Locally recurrent and inoperable or metastatic squamous cell anal cancer
- No prior chemotherapy for advanced disease

Patients should have:
- ECOG 0 to 2

Note: HIV+ patients receiving HAART therapy and CD4 more than or equal to 200; or CD4 less than or equal to 200 with undetectable viral load are eligible

EXCLUSIONS:

Patients must not have:
- ALT and/or AST greater than 10 times the Upper Limit of Normal
- Total bilirubin greater than 128 micromol/L
- Major surgery within 28 days
- Palliative radiation completed within 7 days

CAUTIONS:

- Peripheral neuropathy Grade 2 or higher
- Prior severe arthromyalgia unresponsive to treatment

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium.
- Baseline if clinically indicated: CEA, CA19-9, SCC, GGT, ECG
- Prior to Day 1: CBC & Diff, creatinine, total bilirubin, ALT
- Prior to Day 8 and Day 15: CBC & Diff
- If clinically indicated: CEA, CA19-9, SCC, alkaline phosphatase, albumin, GGT, sodium, potassium, ECG
- For patients on warfarin, weekly INR during treatment until stable warfarin dose established, then INR prior to each cycle

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy protocols as long as CARBOplatin dose is greater than or equal to AUC 4. If CARBOplatin dose is AUC 3, use antiemetic protocol for moderately emetogenic chemotherapy protocols (see SCNAUSEA)
- **PACLitaxel must not be started unless the following drugs have been given:**

  45 minutes prior to PACLitaxel:
  - dexamethasone 10 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to PACLitaxel:

- diphenhydrAMINE 25 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

- **NOTE:** If no PACLitaxel hypersensitivity reaction occurs, no premedications may be needed for subsequent PACLitaxel doses and may be omitted at physician's discretion.
- **NOTE:** If no PACLitaxel hypersensitivity reaction occurs, dexamethasone 8 mg PO may be given on Day 1 of each cycle in place of the regimen in the first bullet point above.
- If hypersensitivity reactions occur, premedications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV premedications given 30 minutes prior to PACLitaxel: dexamethasone 10 mg, diphenhydrAMINE 25 mg, and H_2-antagonist (e.g., famotidine 20 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- ondansetron 8 mg po 30 minutes pre-CARBOplatin of each cycle.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel	80 mg/m^2 once weekly (Days 1, 8, 15)	IV in NS 100 to 500 mL over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
CARBOplatin	Dose = AUC 5 x (GFR** + 25) Day 1 only	IV in NS 100 to 250 mL over 30 minutes

- Repeat every 28 days until disease progression or unacceptable toxicity.

***Measured GFR* (e.g. nuclear renogram) is preferred in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, age greater than 70, etc.). The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR; the estimated GFR reported by the lab or calculated using the Cockcroft-Gault equation should be capped at 125 mL/min when it is used to calculate the initial carboplatin dose. When a nuclear renogram is available, this clearance would take precedence.

Cockcroft-Gault Formula

$$\text{CrCl} = \frac{\text{N (140-age) x weight (kg)}}{\text{serum creatinine (micromol/L)}}$$

Where N = 1.04 for females, and 1.23 for males

Note: The *same* method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

NOTE: Recalculate GFR if, at a point of checking, creatinine increases by greater than 20% or rises above the upper limit of normal

DOSE MODIFICATIONS:

Dose Levels

Agent	Starting Dose	Dose Level -1	Dose Level -2
PACLitaxel	80 mg/m^2	70 mg/m^2	60 mg/m^2
CARBOplatin	AUC 5	AUC 4	AUC 3

1. Hematological Toxicity:

Table 1: Day 1

ANC (x 10^9/L)	CARBOplatin	PACLitaxel
Greater than or equal to 1.5	100 %	100%
1.0 to less than 1.5	Delay until recovery. Then 100 % dose.	Delay until recovery. Then 100 % dose.
0.5 to less than 1.0	Delay until recovery. Then • If recovery in 1 week: 100% dose • If recovery beyond 1 week: reduce by 1 dose level	Delay until recovery. Then 100 % dose.
If at any time: Febrile neutropenia OR ANC less than 0.5 x 10^9/L for 7 or more days	Delay until recovery. Then reduce by 1 dose level.	Delay until recovery. Then reduce by 1 dose level.

Platelets (x 10^9/L)	CARBOplatin	PACLitaxel
Greater than or equal to 100	100 %	100%
75 to less than 100	Delay until recovery. Then 100 % dose	Delay until recovery. Then 100 % dose
50 to less than 75	Delay until recovery. Then • If recovery in 1 week: 100% dose • If recovery beyond 1 week: reduce by 1 dose level	Delay until recovery. Then 100 % dose.
25 to less than 50	Delay until recovery. Then • If recovery in 1 week: 100% dose • If recovery beyond 1 week: reduce by 1 dose level	Delay until recovery. Then • If recovery in 1 week: 100% dose • If recovery beyond 1 week: reduce by 1 dose level
If any time: platelets less than 25 OR bleeding with platelets between 25 to 50 x 10^9/L	Delay until recovery. Then reduce by 1 dose level.	Delay until recovery. Then reduce by 1 dose level.

If treatment is delayed due to hematological toxicity, perform weekly CBC. For recovery beyond 1 week, doses of CARBOplatin and PACLitaxel should be modified according to Day 1 CBC or subsequent CBC if lower.

Table 2: Days 8 and 15 - PACLitaxel

ANC ($\times 10^9$/L)		Platelets ($\times 10^9$/L)	Action
Greater than or equal to 1.0	and	Greater than or equal to 75	100%
Less than 1.0	and/or	Less than 75	Omit

- If hematological toxicity causes omission of only one PACLitaxel administration (Day 8 or Day 15), no dose modification needed for subsequent cycle.
- If hematological toxicity causes omission of both Day 8 and Day 15, doses of PACLitaxel and CARBOplatin should be modified according to Day 8 or Day 15 blood count, whichever is lower as indicated below (Table 3).

Table 3: Subsequent cycle dosing when hematologic toxicity caused omission of BOTH day 8 and day 15 of PACLitaxel

ANC ($\times 10^9$/L) on Day 8 or 15, whichever is lower		Platelets ($\times 10^9$/L) on Day 8 or 15, whichever is lower	Subsequent action	
			CARBOplatin	PACLitaxel
Greater than or equal to 1.0	and	50 to less than 75	Reduce by 1 dose level	No dose modification
	and	25 to less than 50	Reduce by 1 dose level	Reduce by 1 dose level
0.5 to less than 1.0	and	50 to less than 75	Reduce by 1 dose level	No dose modification
	and	25 to less than 50	Reduce by 1 dose level	Reduce by 1 dose level

2. Non-Hematological Toxicity:

Toxicity	PACLitaxel Dose
Motor or sensory neuropathy	Grade 2 : • Interrupt PACLitaxel until neuropathy is resolved to grade 1 or less and decrease dose by one dose level. • If recovery requires more than 2 weeks, omit PACLitaxel from subsequent cycles and continue treatment with CARBOplatin alone. Grade 3 or greater : • Omit PACLitaxel from subsequent cycles and continue treatment with CARBOplatin alone.
Mucositis	Grade 2 : • Hold treatment until mucositis is resolved to grade 1 or less. On recovery, no dose reduction required. Grade 3 or greater : • Hold treatment until mucositis is resolved to grade 1 or less. On recovery, decrease PACLitaxel dose by one dose level. • If mucositis persists at grade 3 or more for more than 2 weeks or recurs despite dose reduction, omit PACLitaxel from subsequent cycles and continue treatment with CARBOplatin alone.

3. Hepatic Dysfunction:

ALT and/or AST	Action
Less than 3 x ULN	PACLitaxel and CARBOplatin at 100 % doses
3 to 5 x ULN	PACLitaxel - reduce by one dose level CARBOplatin – at same dose level
Greater than 5 x ULN	Hold treatment with both drugs until resolution to: • less than 3 x ULN for patients without live metastasis • less than 5 x ULN for patients with liver metastasis and elevated transaminases (3 – 5 x ULN) at the baseline and PACLitaxel - reduce by one dose level CARBOplatin – at same dose level

Bilirubin	Action
Greater than 5 x ULN	• Discontinue paclitaxel • No dose adjustment for carboplatin

ULN = upper limit of normal

4. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia of grade 2 (moderate) or higher was not adequately relieved by NSAIDs or acetaminophen with codeine (e.g., TYLENOL#3®), a limited number of studies report a possible therapeutic benefit using:
   - predniSONE 10 mg PO bid x 5 days starting 24 hours post-PACLitaxel
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 5 to 15 days (based on duration of arthromyalgia)

   If arthralgia and/or myalgia persists, reduce subsequent PACLItaxel doses to 60 mg/m^2

5. Neuropathy: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).

PRECAUTIONS:

1. **Hypersensitivity**: Reactions to PACLitaxel are common. See BC Cancer Hypersensitivity Guidelines

Mild symptoms (e.g., mild flushing, rash, pruritus)	▪ Complete PACLitaxel infusion. Supervise at bedside ▪ No treatment required
Moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension	▪ Stop PACLitaxel infusion ▪ Give IV diphenhydrAMINE 25 to 50 mg and hydrocortisone IV 100 mg ▪ After recovery of symptoms resume PACLitaxel infusion at 20 mL/h for 5 minutes, 30 mL/h for 5 minutes, 40 mL/h for 5 minutes, then 60 mL/h for 5 minutes. If no reaction, increase to full rate. ▪ If reaction recurs, discontinue PACLitaxel therapy
Severe symptoms (i.e., *one* or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	▪ Stop PACLitaxel infusion ▪ Give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ Discontinue PACLitaxel therapy

2. **Extravasation**: PACLitaxel causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Drug Interactions**: PACLitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

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. Rao, S., Sclafani, F., et al. InterAACT, a multicenter open label randomized phase II trial of Cisplatin (CDDP) plus 5 Fluorouracil (5FU) VS Carboplatin (C) plus weekly Paclitaxel (P) in patients with inoperable locally recurrent or metastatic treatment naïve disease: an international rare cancers initiative (IRCI) trial. Abstract 43rd ESMO Congress (ESMO 2018) October 2018, Munich, Germany.
2. Rao, S., Sclafani, F., et al. International Rare Cancers Initiative Multicenter Randomized Phase II Trial of Cisplatin and Fluorouracil Versus Carboplatin and Paclitaxel in Advanced Anal Cancer. InterAAct. JCO 2020, 38 (22):2510-2518.