BC Cancer Protocol Summary for Neoadjuvant Therapy for Penile Squamous Cell Carcinoma Using PACLitaxel, Ifosfamide and CISplatin (TIP)

Protocol Code	*GUOTTIP*
Tumour Group	*Genitourinary*
Contact Physician	*GU Systemic Therapy*

ELIGIBILITY:

Patients must have:
- Squamous cell carcinoma of penis, and
- Multiple or bilateral inguinal node involvement, fixed nodal masses, bulky lymphadenopathy (greater than or equal to 4 cm), or enlarged pelvic nodes on imaging, and
- Planned surgical resection

Patients should have:
- ECOG performance status 0 to 2
- Adequate bone marrow, hepatic and renal function

Note:
- Primary prophylaxis with filgrastim (G-CSF) is not mandatory, but may be considered.

EXCLUSIONS:

Patients must not have:
- Evidence of distant metastatic disease

TESTS:

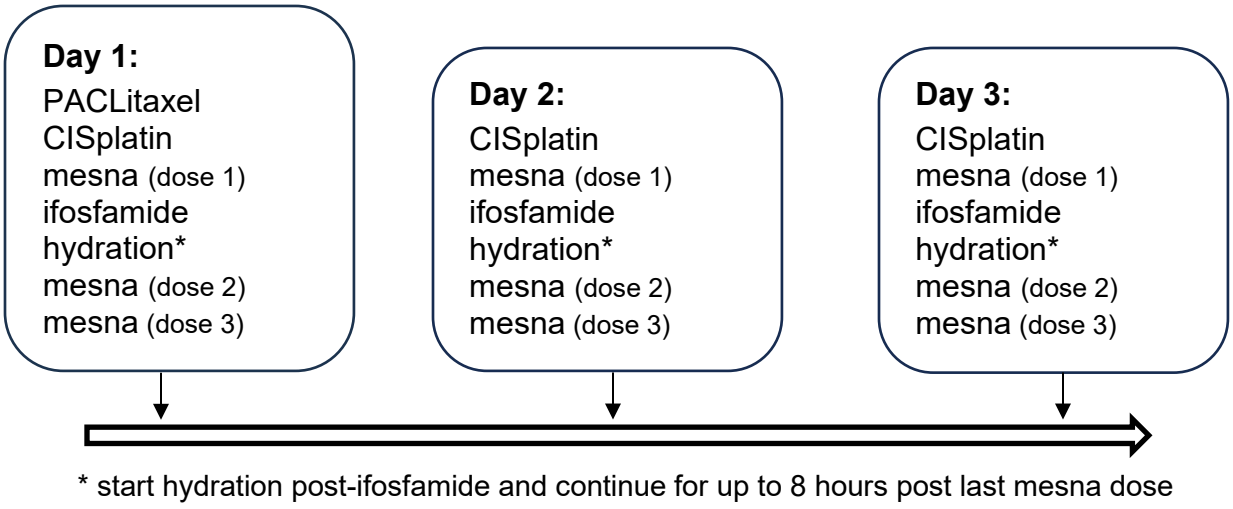
- Baseline: CBC & Diff, creatinine, sodium, potassium, magnesium, phosphate, albumin, ALT, alkaline phosphatase, total bilirubin, random glucose
- Prior to Day 1 of each treatment: CBC & Diff, creatinine, sodium, potassium, magnesium, phosphate, albumin, ALT, alkaline phosphatase, total bilirubin, random glucose
- Prior to treatment on Days 1 to 3: urine dipstick for blood and q8h routinely. If positive, notify MD - see supportive care protocol – SCMESNA
- Vital signs every 8 hours while admitted
- Daily weight (notify MD if weight gain greater than or equal to 4 kg from baseline)
- Daily intake/output (notify MD if urine output is less than 100 mL/hour)
- Record level of consciousness (LOC) every 4 hours. This may include assessment tools such as Glasgow Coma Scale (GCS) and monitoring for neurotoxicity (see Precautions below).

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy protocols (see SCNAUSEA)
- **PACLitaxel must not be started unless the following drugs have been given**:
  45 minutes prior to PACLitaxel:
  - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to PACLitaxel:
  - diphenhydrAMINE 50 mg IV in 50 mL NS over 15 minutes and famotidine 20 mg IV in 100 mL NS over 15 minutes (Y-site compatible)

Treatment Schema:



* start hydration post-ifosfamide and continue for up to 8 hours post last mesna dose

TREATMENT

- **Day 1**:

Hour	Drug	Dose	BC Cancer Administration Guide
0 h	PACLitaxel	175 mg/m^2	IV in 250 to 500 ml NS (use non-DEHP bag) over 3 hours Use non-DEHP tubing with 0.2 micron in-line filter
3 h	CISplatin	25 mg/m^2/day	IV in 100 to 250 mL NS over 30 minutes
3 h 30 min	mesna	400 mg/m^2	IV in 100 mL NS over 15 minutes, before each dose of ifosfamide
3 h 45 min	ifosfamide	1200 mg/m^2/day	IV in 500 mL D5-1/2NS over 2 hours
5 h 45 min	Hydration	After completion of ifosfamide infusion: continue hydration with D5-1/2NS IV at 250 mL/h until post-ifosfamide mesna doses have been administered	
8 h and 12 h	mesna	200 mg/m^2	IV in 100 mL NS over 15 minutes, at both 4 and 8 hours after the start of each dose of ifosfamide
12 h 15 min	Post-hydration	Either: Continue D5-1/2NS IV at 150 mL/h for 8 hours • ONLY patients with hematuria requiring mesna dose adjustments are required to be treated on a 24-hour schedule. OR: Discontinue IV fluids and cap access if patient able to take at least 1 litre of fluids over 8 hours and has not had hematuria • For patients who are hydrating well and have not had hematuria, IV hydration may be discontinued daily after the last mesna dose.	

- **Days 2 and 3**:

Hour	Drug	Dose	BC Cancer Administration Guide
0 h	CISplatin	25 mg/m^2/day	IV in 100 to 250 mL NS over 30 minutes
0 h 30 min	mesna	400 mg/m^2	IV in 100 mL NS over 15 minutes, before each dose of ifosfamide
0 h 45 min	ifosfamide	1200 mg/m^2/day	IV in 500 mL D5-1/2NS over 2 hours
2 h 45 min	Hydration	After completion of ifosfamide infusion: continue hydration with D5-1/2NS IV at 250 mL/h until post-ifosfamide mesna doses have been administered	
5 h and 9 h	mesna	200 mg/m^2	IV in 100 mL NS over 15 minutes, at both 4 and 8 hours after the start of each dose of ifosfamide
9 h 15 min	Post-hydration	Either: Continue D5-1/2NS IV at 150 mL/hr for 8 hours • ONLY patients with hematuria requiring mesna dose adjustments are required to be treated on a 24-hour schedule. OR: Discontinue IV fluids and cap access if patient able to take at least 1 litre of fluids over 8 hours and has not had hematuria • For patients who are hydrating well and have not had hematuria, IV hydration may be discontinued daily after the last mesna dose.	

Repeat every 21 days for 4 cycles.

DOSE MODIFICATIONS:

1. Hematological: for PACLItaxel, CISplatin and ifosfamide

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
Greater than or equal to 1.4	and	Greater than or equal to 100	100%
Less than 1.4	or	Less than 100	Contact Physician. Physician may choose to reduce dose to 85%, add filgrastim (if not already using), or delay treatment*

*This program is given with curative intent. The treating physician may consider the use of filgrastim (G-CSF) to support timely delivery of full-dose treatment. Treatment cycles may be administered within a 21 to 28-day interval to allow for hematologic recovery, based on clinical judgment and patient tolerance.

2. Renal dysfunction: for CISplatin

Creatine clearance (mL/min)	CISplatin dose
Greater than 40 mL/min	100%
Less than or equal to 40 mL/min	Contact Physician. Physician may choose to reduce dose to 85%, step up hydration, or delay treatment

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance (mL/min)} = \frac{1.23 \times (140 - \text{age}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

3. **Hepatic dysfunction**: Dose modification required for PACLitaxel. Refer to BC Cancer Drug Manual.

4. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia from PACLitaxel of Grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDS or acetaminophen with codeine (TYLENOL #3), a limited number of studies report a possible therapeutic benefit from the following:
    - predniSONE 10 mg PO BID for 5 days starting 24 hours post PACLitaxel
    - gabapentin 300 mg PO on day prior to PACLitaxel, 300 mg PO BID on treatment day and then 300 mg PO TID for 7 to 10 days

5. **Neuropathy**: Dose modification or discontinuation for PACLitaxel may be required. Refer to BC Cancer Drug Manual.

PRECAUTIONS:

1. **Febrile neutropenia**: Consider prophylactic filgrastim per discretion of the treating physician. Febrile neutropenia can result in serious patient harm, treatment delays, and hospitalization. Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.

2. **Hypersensitivity**: Reactions are common with PACLitaxel. Refer to 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

3. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside.

4. **CNS toxicity:** ifosfamide can cause encephalopathy (manifest as confusion, lethargy, seizures or coma). Avoid CNS depressant medications. If drowsiness develops while receiving ifosfamide, discontinue all sedating medications and continue ifosfamide. If patient is confused, not arousable or comatose, discontinue ifosfamide. If ifosfamide is the cause of CNS depression, then it should not be given again. If the CNS changes are not due to ifosfamide, then ifosfamide can be reinstituted providing the previous medications contributing to CNS toxicity are not given again with it. If a seizure occurs on ifosfamide, then that cycle should be discontinued. Further cycles may be given if the patient is on anticonvulsants.

Contact the GU Systemic Therapy physician at your regional cancer centre or the GU Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Pagliaro LC, Williams DL, Daliani D, Williams MB, Osai W, Kincaid M, Wen S, Thall PF, Pettaway CA. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. J Clin Oncol. 2010 Aug 20;28(24):3851-7.
2. Pettaway CA, Pagliaro L, Theodore C, Haas G. Treatment of visceral, unresectable, or bulky/unresectable regional metastases of penile cancer. Urology. 2010 Aug;76(2 Suppl 1):S58-65.