Regimen Monograph

A - Regimen Name

TIP Regimen

Paclitaxel-Ifosfamide (with Mesna)-Cisplatin

Disease Site	Genitourinary - Testis
Intent	Curative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Treatment of relapsed testicular germ cell tumours. This was studied in a phase II trial involving patients who failed to achieve a continuous CR to a prior platinum-based regimen, and have other prognostic features for achieving a favourable outcome to conventional-dose cisplatin-based salvage chemotherapy.

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B - Drug Regimen

Adapted for outpatient administration:

PACLitaxel	250 mg /m²	IV over 3 hours	Day 1
mesna	500 mg /m²	IV immediately before ifosfamide	Days 2 to 5
ifosfamide	1500 mg /m²	IV	Days 2 to 5
CISplatin	25 mg /m²	IV	Days 2 to 5
mesna	500* mg /m²	IV at 4 and 8 hours post-ifosfamide	Days 2 to 5

(*or mesna 1000 mg/m^2 PO)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a maximum of 4 cycles, unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low (D1)
Moderate (D2-5)

Febrile Neutropenia Risk: High

Other Supportive Care:

Paclitaxel: Patients should be pretreated with a corticosteroid as well as an antihistamine and a H2 blocker: For example:

- DEXAMETHASONE 20mg PO 12 & 6 hours or 20mg IV 30 minutes before paclitaxel
- DIPHENHYDRAMINE 50mg IV 30 minutes before paclitaxel
- RANITIDINE 50mg IV 30 minutes before paclitaxel

Standard regimens for Cisplatin premedication and hydration should be followed. Refer to local

guidelines.

Ifosfamide: Oral/IV hydration is strongly encouraged. Poorly hydrated patients may need more IV hydration. Inadequate total hydration may result in dose-related hemorrhagic cystitis.

Filgrastim 5 mcg /kg SC on days 7 to 18 (until ANC > 1 x 10^9/L) has been used in clinical trials.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

There were no dose reductions in the clinical trial. Recovery from toxicities were required before re-treatment with a subsequent cycle.

Worst Toxicity / Counts (x 10^9/L) in previous cycle	**PACLitaxel (% previous dose)**	**ifosfamide (% previous dose)**	**cisplatin (% previous dose)**
Somnolence or other signs of encephalopathy	100%	Hold; methylene blue 50mg IV q4h until resolution. Consider prophylactic methylene blue for subsequent cycles, or consider discontinuing for next cycle	100%
Hematuria	100%	Hold until resolution if microscopic; if macroscopic reduce dose or discontinue	100%
Grade 3 neurotoxicity	Discontinue		
Grade 4 related organ / non-hematologic	Discontinue		

*In the clinical trial, re-treatment with a subsequent cycle required a neutrophil count of ≥ 0.45 x 10^9/L and a platelet count of ≥ 75 x 10^9/L.

Paclitaxel - Dosage after Hypersensitivity:

- **For mild symptoms** (e.g., mild flushing, rash, pruritus) attempt to complete the infusion under close supervision.
- **For moderate symptoms** (e.g., moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension),
  - Stop the paclitaxel infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125 mg IV.
  - Once symptoms have resolved, resume paclitaxel infusion at a rate of 10% of original rate for 15 minutes, then at 25% of original rate for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete.
- **For severe symptoms** (e.g., one or more of: respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy),
  - Stop the paclitaxel infusion; give diphenhydramine and methylprednisolone as above. Use epinephrine or bronchodilators if indicated.
  - Do not rechallenge with paclitaxel.

Filgrastim: Hold ± discontinue for ARDS or alveolar hemorrhage.

Hepatic Impairment

Bilirubin		**AST/ALT**	**PACLitaxel**	**ifosfamide** **(% previous dose)**	**cisplatin** **(% previous dose)**
1-2 x ULN	and/or	< 2 x ULN		100%	No change
>2-4 x ULN	and/or	2-5 x ULN	↓ to 135mg/m2	75%	No change
>4 x ULN	and/or	> 5 x ULN	↓ to 50mg/m2 or omit	Discontinue	No change

Renal Impairment

Creatinine Clearance (mL/min)	**PACLitaxel** **(% previous dose)**	**ifosfamide** **(% previous dose)**	**cisplatin** **(% previous dose)**

>60	No change	100%	100%
>45-60	No change	75%	75%
>30-45	No change	50%	50%
20-30	No change	50%	Discontinue
<20	No change	Discontinue	Discontinue

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F - Adverse Effects

Refer to PACLitaxel, mesna, ifosfamide, CISplatin, filgrastim drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± infection / bleeding (may be severe) • Nausea and vomiting • Nephrotoxicity (may be severe) • Electrolyte abnormalities • Neurotoxicity and ototoxicity (may be severe) • Hemorrhagic cystitis (may be severe) • Diarrhea, mucositis • Edema • Fatigue • Myalgia, arthralgia • Increases in LFTs (may be severe) • Alopecia	• Hemolytic uremic syndrome, vasculitis • AML, MDS • Hypersensitivity (may be severe) • Raynaud's • Arrhythmia, cardiac failure • Arterial, venous thromboembolism • Pancreatitis • GI perforation, obstruction • Pneumonitis • Seizure • Encephalopathy • Cardiotoxicity • DIC • SIADH • Rhabdomyolysis • Renal tubular acidosis / Fanconi syndrome

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G - Interactions

Refer to PACLitaxel, mesna, ifosfamide, CISplatin, filgrastim drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to PACLitaxel, mesna, ifosfamide, CISplatin, filgrastim drug monograph(s) for additional details

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and regular
- Liver function tests; baseline and regular
- Renal function tests, baseline and regular
- Urinalysis, for RBCs; before each ifosfamide dose and regular
- Electrolytes, including magnesium, phosphate and calcium; baseline and regular
- Blood pressure and pulse rate monitoring during infusion, cardiac monitoring with prior arrhythmia;
- Clinical toxicity assessment (infection, bleeding, musculoskeletal pain, thromboembolism, cutaneous effects, hypersensitivity, cystitis, nausea/vomiting, neurotoxicity, ototoxicity); at each visit
- Audiogram; as clinically indicated
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- CBC; 2-3 times a week during filgrastim therapy

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J - Administrative Information

Approximate Patient Visit	Day 1: 5 hours; Days 2-5: 5.5 hours
Pharmacy Workload (average time per visit)	39.119 minutes
Nursing Workload (average time per visit)	53.167 minutes

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K - References

Feldman DR, Hu J, Dorff TB, et al. Paclitaxel, Ifosfamide, and Cisplatin Efficacy for First-Line Treatment of Patients With Intermediate- or Poor-Risk Germ Cell Tumors. J Clin Oncol 2016;34(21):2478-83.

Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;;23(27):6549-55.

Mead GM, Cullen MH, Huddart R, et al. A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial. Br J Cancer 2005;93(2):178-84.

Motzer RJ, Sheinfeld J, Mazumdar M, et al. Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. J Clin Oncol 2000 Jun;18(12):2413-8.

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M - Disclaimer

Regimen Abstracts

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Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not

undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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