# PACLitaxel, Ifosfamide, and CISplatin (TIP) Therapy

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | HSE approved reimbursement status* |
|---|---|---|---|
| Treatment of relapsed / refractory metastatic testicular germ cell cancer | C62 | 00602a | N/A |

*This is for post 2012 indications only

## TREATMENT:

*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.*

PACLitaxel is administered on Day 1; CISplatin, ifosfamide and mesna are administered on Days 1 to 5. Treatment is administered every 21 days for 4 cycles.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

| Admin. Order | Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|---|
| 1 | 1 | PACLitaxel[a,b] | 175mg/m$^2$ | IV infusion | 500mL 0.9% NaCl over 3 hours | Every 21 days for 4 cycles |
| 2 | 1-5 | CISplatin | 20mg/m$^2$ | IV infusion | 1000mL 0.9% NaCl over 1 hour (Pre hydration therapy required)[c] | Every 21 days for 4 cycles |
| 3 | 1-5 | Mesna | 400mg/m$^2$ | IV infusion | 100mL NaCl 0.9% over 15 minutes immediately before the infusion of ifosfamide | Every 21 days for 4 cycles |
| 4 | 1-5 | Ifosfamide[d] | 1200mg/m$^2$ | IV infusion | 1000mL 0.9% NaCl over 2 hours | Every 21 days for 4 cycles |
| 5 | 1-5 | Mesna | 400mg/m$^2$ | IV infusion | 100mL NaCl 0.9% over 15 minutes at 4 hours after completion of ifosfamide infusion | Every 21 days for 4 cycles |
| 6 | 1-5 | Mesna | 400mg/m$^2$ | IV infusion | 100mL NaCl 0.9% over 15 minutes at 8 hours after completion of ifosfamide infusion | Every 21 days for 4 cycles |
| 1 | 6 | G-CSF | 5mcg/kg | SC (round to nearest whole syringe) | Continue until neutrophil recovery **(Refer to local policy)** | |

[a] PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.

[b] PACLitaxel should be diluted to a concentration of 0.3-1.2mg/mL.

[c] **Pre-hydration therapy required for CISplatin**

See local hospital policy for recommendations.

Suggested Pre-hydration for CISplatin therapy:

Administer 10mmol magnesium sulphate (MgSO4) (+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 – 120 minutes (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above.

[d] **Ifosfamide Hydration: (Refer to local policy or see suggested hydration below)**

Ensure patient receives at least 3L of IV or oral fluids per day.

Furosemide should also be administered if required to ensure a urinary output of at least 100mL/hour.

Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mLs or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide.

## ELIGIBILITY:

- Indications as above
- ECOG status 0-2

## EXCLUSIONS:

- Hypersensitivity to PAClitaxel, CISplatin, ifosfamide, mesna, or any of the excipients
- CISplatin
  - Pre-existing neuropathies ≥ grade 2
  - Severe renal impairment
  - Significant hearing impairment/tinnitus
- PAClitaxel
  - Severe hepatic impairment
  - Baseline neutrophil count < 1.5 x $10^9$/L

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

## TESTS:

**Baseline tests:**

- FBC, renal and liver profile
- Audiology and creatinine clearance if clinically indicated

**Regular tests:**

- FBC, renal and liver profile prior to each treatment
- Assess neurological function daily while on ifosfamide
- Check urinalysis for haematuria prior to ifosfamide and daily during treatment with ifosfamide

**Disease monitoring:**

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

## Haematological:

- All delays to treatment must be approved by prescribing consultant.

**Table 1: Dose modification of PACLitaxel in haematological toxicity**

| ANC ($x10^9$/L) | | Platelets ($x10^9$/L) | Dose |
|---|---|---|---|
| ≥1.0 | and | ≥90 | 100% dose |
| <1.0 | or | <90 | Delay. If no recovery after 1 week, reduce dose by 25% (or 50% in severe cases) |

**Table 2: Dose modification of ifosfamide in haematological toxicity**

| ANC ($x10^9$/L) | | Platelets ($x10^9$/L) | Dose |
|---|---|---|---|
| ≥1.0 | and | ≥75 | 100% dose |
| <1.0 | or | <75 | Delay. If no recovery after 1 week, reduce dose by 25% (or 50% in severe cases) |

## Renal and Hepatic Impairment:

**Table 3: Dose modification in renal and hepatic impairment**

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td rowspan="5">PAClitaxel</td><td colspan="2" rowspan="5">No need for dose adjustment is expected<br><br>Haemodialysis: no need for dose adjustment is expected</td><td>ALT</td><td></td><td>Total bilirubin</td><td>Dose of PAClitaxel</td></tr>
<tr><td>< 10 x ULN</td><td>and</td><td>≤ 1.25 x ULN</td><td>100% dose</td></tr>
<tr><td>< 10 x ULN</td><td>and</td><td>1.26-2 x ULN</td><td>75% of original dose</td></tr>
<tr><td>< 10 x ULN</td><td>and</td><td>2.01-5 x ULN</td><td>50% of original dose</td></tr>
<tr><td>≥ 10 x ULN</td><td>and/or</td><td>> 5 x ULN</td><td>Contraindicated</td></tr>
<tr><td rowspan="6">CISplatin</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="4" rowspan="6">No need for dose adjustment is expected</td></tr>
<tr><td>≥ 60</td><td>100%</td></tr>
<tr><td>50-59</td><td>75%</td></tr>
<tr><td>40-49</td><td>50%</td></tr>
<tr><td>< 40</td><td>Not recommended</td></tr>
<tr><td>Haemodialysis</td><td>50% of the original dose may be considered</td></tr>
</table>

<table>
<tr><td rowspan="4">Ifosfamide</td><td>CrCL (mL/min)</td><td>Dose</td><td rowspan="4">Mild and moderate: no need for dose adjustment is expected<br><br>Severe: not recommended, due to risk of reduced efficacy. Dose reductions are probably not necessary for patients with altered liver function. However ifosfamide is extensively hepatically metabolised and some clinicians recommend a 25% dose reduction for patients with significant hepatic dysfunction (serum AST > 300units/L or bilirubin > 51.3 micromol/L. Clinical decision.</td></tr>
<tr><td>≥50</td><td>No dose adjustment is needed</td></tr>
<tr><td><50</td><td>Not recommended</td></tr>
<tr><td>Haemodialysis</td><td>Not recommended</td></tr>
<tr><td colspan="4">PACLitaxel (renal and hepatic - Giraud et al 2023)<br>CISplatin (renal and hepatic - Giraud et al 2023)<br>Ifosfamide (renal - Giraud et al 2023; hepatic - based on Giraud et al 2023 and as agreed by lead reviewer)</td></tr>
</table>

### Management of adverse events:

**Table 4: Dose modification schedule for PACLitaxel based on adverse events**

| Adverse reactions | Recommended dose modification |
|---|---|
| Grade 2 motor or sensory neuropathy | Dose reduction or delay in treatment may be required. |
| ≥ Grade 3 reaction | Discontinue |

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

PAClitaxel Low **(Refer to local policy).**
CISplatin High (**Refer to local policy).**
Ifosfamide Moderate **(Refer to local policy).**

- Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.

### PREMEDICATIONS:

- Hydration prior to CISplatin administration **(Refer to local policy or see recommendations above).**
- All patients must be premedicated with corticosteroids, antihistamines, and H2 antagonists prior to first dose of PACLitaxel treatment.
- The $H_2$ antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.

- Where a patient experiences hypersensitivity, consider the use of alternative $H_2$ antagonists **(Refer to local policy).**

Table 5 outlines suggested premedications prior to treatment with PACLitaxel.

**Table 5: Suggested premedications prior to treatment with PACLitaxel**

| Drug | Dose | Administration prior to PACLitaxel |
|---|---|---|
| dexAMETHasone | 20mg oral or IV[a,b] | For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes |
| Chlorphenamine | 10mg IV | 30 minutes |
| Famotidine[c] | 20mg IV | 30 minutes |
| [a]Dose of dexAMETHasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance. | | |
| [b]If aprepitant is added to the anti-emetic regimen, consideration should be given to reducing the dose of dexAMETHasone to 12mg on the day of treatment. | | |
| [c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance. | | |

## OTHER SUPPORTIVE CARE:

- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

*The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details*.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. Avoid aminoglycoside antibiotics.

**PACLitaxel**

- **Hypersensitivity:** Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug**.**
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated **(Refer to local policy).**
- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days.

- **Cardiac conduction abnormalities:** If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.

**CISplatin**

- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage**: These are associated with CISplatin. They should be assessed by history prior to each cycle.
- **Hypersensitivity**: Hypersensitivity reaction have been reported with CISplatin.

**Ifosfamide**

- **Ifosfamide-induced encephalopathy:** This may occur in patients treated with high doses of ifosfamide. Neurological function should be assessed prior to each ifosfamide dose.
- **Renal and urothelial toxicity:** Ifosfamide is both nephrotoxic and urotoxic. Glomerular and tubular kidney function must be evaluated and checked before commencement of therapy, as well as during and after treatment. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity. During or immediately after administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna. Ifosfamide should be used with caution, if at all, in patients with active urinary tract infections.

## DRUG INTERACTIONS:

- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concurrent administration of CISplatin and phenytoin may result in decreased serum levels of phenytoin. In these patients, monitor plasma levels of phenytoin and dose adjust accordingly.
- Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.
- Avoid concurrent use of ifosfamide with nephrotoxic drugs (e.g. aminoglycosides, NSAIDS) due to additive nephrotoxicity.

- Current drug interaction databases should be consulted for more information.

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