

## PACLITAXEL IFOSFAMIDE CISPLATIN (TIP)

### INDICATION (ICD10) C62

1. Salvage for metastatic germ cell, metastatic seminoma

### REGIMEN

Day 1 Premedication 30 minutes prior to infusion:  
Dexamethasone 20mg IV bolus  
H<sub>2</sub> antagonist  
Chlorphenamine 10mg IV bolus  
PACLITAXEL 175mg/m<sup>2</sup> in 500ml\* sodium chloride 0.9% IV infusion over 3 hours  
Prehydration  
CISPLATIN 20mg/m<sup>2</sup> IV in 1000ml sodium chloride 0.9% infusion over 1 hour  
Mesna 200mg/m<sup>2</sup> in 250ml sodium chloride 0.9% infusion over 30 minutes  
IFOSFAMIDE 1000mg/m<sup>2</sup> with Mesna 1000mg/m<sup>2</sup> in 1000ml sodium chloride 0.9% infusion over 1 hour  
Mesna 600mg/m<sup>2</sup> in 500ml sodium chloride 0.9% over 12 hours

Days 2 to 5

Prehydration  
CISPLATIN 20mg/m<sup>2</sup> IV in 1000ml sodium chloride 0.9% infusion over 1 hour  
Mesna 200mg/m<sup>2</sup> in 250ml sodium chloride 0.9% infusion over 30 minutes  
IFOSFAMIDE 1000mg/m<sup>2</sup> with Mesna 1000mg/m<sup>2</sup> in 1000ml sodium chloride 0.9% infusion over 1 hour  
Mesna 600mg/m<sup>2</sup> in 500ml sodium chloride 0.9% over 12 hours

\* doses 84mg to 144mg in 250ml sodium chloride 0.9%

### CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days for 4 cycles

### ANTI-EMETICS

High emetogenic risk days 1 to 5

### CONCURRENT MEDICATION REQUIRED

Cisplatin	Ensure adequate pre and post hydration. If urine output is <100 ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40 mg furosemide PO/IV.
Ifosfamide	Ensure mesna administered
Paclitaxel	Ensure premedication given before paclitaxel
GCSF	Consider GCSF

### EXTRAVASATION AND TYPE OF LINE / FILTERS

Cisplatin – exfoliant  
Ifosfamide - neutral  
Paclitaxel – vesicant

Administer paclitaxel via polyethylene lined administration set with ≤0.22micron filter  
Peripheral line

## INVESTIGATIONS

Blood results required before SACT administration  
 FBC, U&E and LFTs every week  
 Neutrophils  $\times 10^9/L \geq 1.0$  (adjuvant or neoadjuvant use)  
 Platelets  $\times 10^9/L \geq 100$   
 Serum creatinine every cycle  
 Baseline weight and every cycle

## MAIN TOXICITIES AND ADVERSE REACTIONS

Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Ifosfamide	Ifosfamide encephalopathy.
Paclitaxel	(2% risk of severe hypersensitivity) Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10 minutes), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.

## INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS (not exhaustive list check SPC/BNF/Stockleys)

Cisplatin	Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Cisplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.
Ifosfamide	Aprepitant and fosaprepitant are predicted to increase the exposure to ifosfamide. Caution.
Paclitaxel	DOACs to be used with caution, need dose modifications or to be avoided eg apixaban Clopidogrel interacts with paclitaxel potentially increasing the concentration of paclitaxel. Paclitaxel is catalysed, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. inhibitors (e.g. erythromycin, fluoxetine, gemfibrozil) use with caution. inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) use with caution.

## DOSE MODIFICATIONS

### Non-haematological

#### Paclitaxel

If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration.

If grade  $\geq 2$  neuropathy, consider giving 75% dose

If grade  $>3$  peripheral neuropathy is  $>$  grade 3 omit further paclitaxel

## Ifosfamide

### Neural toxicity grade

Toxicity Grade	Tp/C <sub>crea</sub> (T <sub>mp</sub> /GFR) (mmol/l)	HCO <sub>3</sub> <sup>*</sup> (mmol/l)	Action (apply worst grade)
Grade 0/1	≥1.00	≥17.0	give 100% dose
Grade 2	0.8-0.99	14.0-16.9	give 70% of total dose
Grade 3/4	≤0.8	≤14.0	**Switch to cyclophosphamide

\*Low values of HCO<sub>3</sub> should be re-checked when the patient is clinically stable (to rule out infection as a cause, etc) before modifying treatment.

\*\*Discuss with consultant before and to confirm substitution of ifosfamide with cyclophosphamide 1500mg/m<sup>2</sup>/day.

### Fractional phosphate clearance calculated

$$\text{Tp/C}_{\text{crea}} [\text{mmol/ml}] = \text{Phosphate}_{\text{serum}} - \frac{\text{Phosphate}_{\text{urine}} \times \text{creatinine}_{\text{serum}}}{\text{Creatinine}_{\text{urine}}}$$

## Hepatic impairment

### Ifosfamide

Severe impairment	not recommended
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### Paclitaxel

In the absence of Gilbert's syndrome:

Transaminase <10xULN and bilirubin ≤1.25xULN	no dose reduction
Transaminase <10xULN and bilirubin 1.26-2xULN	give 77% of original dose
Transaminase <10xULN and bilirubin 2.01-5xULN	give 51% of original dose
Transaminase ≥10xULN or bilirubin >5xULN	contraindicated

## Renal impairment

### Cisplatin

CrCl >60ml/min	give 100% dose
CrCl 45-60ml/min	give 75% dose
CrCL<45ml/min	not recommended

### Ifosfamide

CrCl <50ml/min	not recommended
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## REFERENCES

1. Mead G et al on behalf of the MRC Testicular tumour working party. A phase 2 trial of TIP given as second line (post BEP)
2. Salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial. British Journal of Cancer (2005) 93, 178-184
3. Motzer RJ et al Paclitaxel, ifosfamide and cisplatin second line therapy for patients with relapsed testicular germ cell cancer. J Clin Oncol 18: 2413-2418