PACLITAXEL IFOSFAMIDE CISPLATIN (TIP) (3 day)

INDICATION (ICD10) C60

1. A first-line option for suitable patients with advanced penile cancer

REGIMEN

Day 1
Premedication 30 minutes prior to infusion:
Dexamethasone 20mg IV bolus
Chlorphenamine 10mg IV bolus
PACLITAXEL 175mg/m^2 in #ml sodium chloride 0.9% IV infusion over 3 hours
Prehydration
CISPLATIN 25mg/m^2 IV in #ml sodium chloride 0.9% infusion over 1 hour
Mesna 400mg/m^2 in #ml sodium chloride 0.9% infusion over 15 minutes
IFOSFAMIDE 1200mg/m^2 with Mesna 1200mg/m^2 in #ml sodium chloride 0.9% infusion over 2 hours
Mesna 800mg/m^2 in #ml sodium chloride 0.9% over 8 hours

Days 2 and 3
Prehydration
CISPLATIN 25mg/m^2 IV in #ml sodium chloride 0.9% infusion over 1 hour
Mesna 400mg/m^2 in #ml sodium chloride 0.9% infusion over 15 minutes
IFOSFAMIDE 1200mg/m^2 with Mesna 1200mg/m^2 in #ml sodium chloride 0.9% infusion over 2 hours
Mesna 800mg/m^2 in #ml sodium chloride 0.9% over 8 hours

diluent and diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days for 4 cycles

ANTI-EMETICS

High emetogenic risk days 1 to 3

CONCURRENT MEDICATION REQUIRED

Cisplatin	Ensure adequate pre and post hydration. If urine output is <100ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40mg 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 or DEHP free administration set with ≤0.22micron filter
Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E including $Mg^{++}$and LFTs every cycle
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥100
Serum creatinine every cycle
Baseline weight and every cycle

MAIN TOXICITES 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

Cisplatin
If patient complains of tinnitus, tingling of fingers and/or toes, discuss with SpR or Consultant before administration.

Paclitaxel
If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration.
If grade ≥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_{crea} (Tm_p/GFR) (mmol/l)	HCO_3* (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_3 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^2/day.

Fractional phosphate clearance calculated

$$Tp/C_{crea}\ [mmol/ml] = Phosphate_{serum} - \frac{Phosphate_{urine} \times creatinine_{serum}}{Creatinine_{urine}}$$

Hepatic impairment
Cisplatin
No need for dose adjustment.

Ifosfamide

Severe impairment	not recommended

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 50-59ml/min	give 75% dose
CrCl 40-49ml/min	give 50% dose (curative intent) not recommended (palliative intent)
CrCL<40ml/min	not recommended

Ifosfamide

CrCl <50ml/min	not recommended

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