TIP (Paclitaxel, Ifosfamide and Cisplatin)

Indication

First line treatment for relapsed metastatic seminoma, non seminoma or combined tumours. Where appropriate consider patients for high dose chemotherapy.

ICD-10 codes

Codes pre-fixed with C38, C48, C56, C62, C63, C75.3.

Regimen details

Day	Drug	Dose	Route
1	Paclitaxel	175mg/m^2	IV infusion
1 – 5	Cisplatin	20mg/m^2	IV infusion
1	Mesna	200mg/m^2	IV bolus
1 - 5	Ifosfamide and Mesna	1 g/m^2 and 500mg/m^2	IV infusion
1 - 5	Mesna	500mg/m^2	IV infusion

Cycle frequency

21 days

Number of cycles

Usual maximum 4 cycles. Consultant/MDT decision to give further cycles.

Administration

Paclitaxel is administered in a 500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 3 hours. Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of paclitaxel. Facilities for the treatment of hypotension and bronchospasm **must** be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel and appropriate therapy should be initiated

Cisplatin is administered in 500mL sodium chloride 0.9% over 60 minutes following the pre and post hydration protocol below.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	1 hour
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	30 minutes 30 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. If a patient develops fluid retention i.e. weight gain >2.5kg or urine output < 100ml/ hour during treatment give a single dose of 20mg furosemide or mannitol (200mL mannitol 20% OR 400mL mannitol 10%). Do not give more than a single dose of either furosemide or mannitol without discussing with consultant.		
Cisplatin	500mL	1 hour
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700mL or 2900mL**	**4 hours 30 minutes**

Note: Patients with magnesium or potassium below the normal range should have 2g $MgSO_4$ and 20mmol KCl added to the pre-hydration bag and the duration of the infusion increased to 2 hours.

All patients must be advised to drink at least 2 litres of fluid over the following 24 hours.

On day 1 mesna is given as a slow bolus immediately prior to the ifosfamide infusion.

Ifosfamide and mesna are administered together as an IV infusion in 500mL sodium chloride 0.9% over 60 minutes. This is immediately followed by mesna 500mg/m2 in 500mL sodium chloride 0.9% administered as an IV infusion over 8 hours.

Pre-medication

30 minutes prior to paclitaxel:

Chlorphenamine 10mg IV slow bolus
Dexamethasone 16-20mg IV slow bolus

Emetogenicity

This regimen has severe emetic potential.

Additional supportive medication

Consider allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.
Oral magnesium supplementation between cycles in addition to the intravenous magnesium administered at the time of chemotherapy if required as per local magnesium replacement guidelines.
Anti-emetics as per local policy.
GCSF as primary prophylaxis from day 6
Mesna if required for haemorrhagic cystitis (see toxicities below).

Extravasation

Paclitaxel is vesicant (Group 5)
Cisplatin is an exfoliant (Group 4)
Ifosfamide is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
AFP, HCG, LDH	14 days (repeat on day 1)
LH, FSH and testosterone	28 days
CXR	28 days
Audiology	28 days

Formal EDTA measurement of creatinine clearance is recommended.

Where appropriate offer pre-treatment sperm storage.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
AFP, HCG, LDH	7 days (repeat weekly during treatment)

Repeat audiology if patient reports hearing loss or persistent tinnitus.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
WBC	≥ 1.5 x 10^9/L*
Neutrophils	≥ 0.5 x 10^9/L*
Platelets	≥ 75 x 10^9/L*
Calculated CrCl	> 60 ml/min
Bilirubin	< ULN
ALT/ALT	< 2.5 x ULN
Alkaline phosphatase	< 2.5 x ULN

*Prior to day one only.

If, on day one, WBC < 1.5 x 10^9/L, neutrophils < 0.5 x 10^9/L or platelets < 75 x 10^9/L delay for 3 days and if recovered resume at full doses. If not, repeat FBC every 3 days and start treatment when counts have recovered. If more than 3 days delay discuss with consultant about modifying doses. Modifications of cisplatin dose are not usually required for myelosuppression

If doses are reduced for one cycle, each subsequent cycle should be assessed independently based on the FBC on day 1 of that cycle. Dose modifications for myelosuppression are not usually carried forward to the next cycle.

Dose modifications

- **Renal impairment**

Full dose cisplatin should be administered if calculated CrCl is > 60ml/min. An EDTA creatinine clearance should be repeated if CrCl falls below this value. Discuss with consultant about modifying dose of cisplatin or substituting with carboplatin.

CrCl (mL/min)	**Cisplatin dose**	**Ifosfamide dose**
>60	100%	100%
51 – 60	75%	70%
40 – 50	50%	
<40	Discuss with consultant – consider carboplatin	Consultant decision

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Paclitaxel dose**
<1.5	and	< 2.5	100%
1.5-3.0	or	2.5-4.0	50 - 75% (consultant decision)
>3.0	or	> 4.0	25% or omit (consultant decision)

No dose modification required for cisplatin.

If bilirubin > ULN or AST/ALT or alkaline phosphatase > 2.5 x ULN ifosfamide is contraindicated – discuss with consultant.

- **Other toxicities**

Paclitaxel:

Toxicity	**Definition**	**Paclitaxel dose**
Fatigue	Grade 3	1st occurrence – 75% (consultant decision)
Neuropathy	Grade 2	1st occurrence – 75% if persistent 50% or discontinue. Discuss with consultant.
	Grade ≥ 3	Withhold until ≤ grade 1, restart at 50%.
Arthralgia/Myalgia	Grade ≥ 2	If persists reduce dose to 75%. Discuss with consultant

Cisplatin:

Toxicity	**Definition**	**Dose adjustment**
Neurotoxicity	Grade 2	Discuss with consultant
	Grade 3-4	Discontinue
Ototoxicity	Grade 2	Discuss with consultant
	Grade 3-4	Discontinue

Ifosfamide:

Haemorrhagic cystitis: urine dipstick should be monitored every 4 hours during treatment. If positive (and other causes of haematuria have been excluded) additional mesna should be prescribed as per table below:

Dipstick blood result	**Action**
Trace	Re-test
+	Re-test, if positive on more than one consecutive test, give additional bolus mesna dose (20% of daily ifosfamide dose)
++	Give bolus mesna dose and double mesna infusion dose – discuss with consultant
+++	Give bolus mesna dose and double mesna infusion dose – discuss with consultant

Patients should be encouraged to drink plenty.

If a patient suffers haemorrhagic cystitis, consider increasing mesna dose for next cycle.

Encephalopathy: ifosfamide can cause encephalopathy. If ≥ grade 2 encephalopathy, the ifosfamide infusion should be stopped immediately. Methylene blue should be commenced IV 50mg 4 hourly until symptoms have resolved to grade 0.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Nephrotoxicity
Ototoxicity
Neurotoxicity
Encephalopathy
Haemorrhagic cystitis
Infertility
Arrhythmias
Pulmonary fibrosis
Secondary malignancy
Long term risk of cardiovascular disease and metabolic syndrome
Osteonecrosis of the hip

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Stomatitis, mucositis
Alopecia
Nausea and vomiting
Anorexia

- **Other side effects**

Electrolyte disturbances
Fatigue
Headache

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Antibiotics: The renal toxicity of cisplatin is potentiated by aminoglycoside antibacterials (e.g. gentamicin) and amphotericin. Aminoglycosides should be avoided. If aminoglycosides are prescribed, close monitoring of renal function and serum antibiotic levels is required.

Avoid all nephrotoxic drugs where possible

Paclitaxel:
Clozapine: increased risk of agranulocytosis

Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Additional comments

This regimen may be given as an inpatient or day case as per local practice.

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed 2 December 2015 2015 via www.medicines.org.uk
- Summary of Product Characteristics Ifosfamide (Baxter) accessed 2 December 2015 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Hospira) accessed 2 December 2015 2015 via www.medicines.org.uk
- Mead G, Cullen M, Huddart R, Harper P, Rustin G, Cook P, Stenning S and Mason M on behalf of the MRC Testicular Tumour Working Party. 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. British Journal of Cancer (2005) 93, 178-184
- Motzer RJ, Sheinfeld J, Mazumdar M, Bains M, Mariani T, Bacik J, Bajorin D & Bosl GJ. (2000) Paclitaxel, ifosfamide and Cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. J Clin Oncol 18: 2413−2418

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Date: April 2016 v2 December 2018