Systemic Anti Cancer Treatment Protocol

TIP
Paclitaxel, Ifosfamide and Cisplatin

PROTOCOL REF: MPHATIPGC
(Version No: 1.1)

Approved for use in:

Second line treatment of germ cell tumours

Dosage:

Drug	Dosage	Route	Frequency
Paclitaxel	175mg/m^2	IV	Day 1
Cisplatin	20mg/m^2	IV	Days 1 to 5
Ifosfamide	1000mg/m^2	IV	Days 1 to 5

Supportive treatments:

Mesna – see administration details

Domperidone 10mg oral tablets, to be taken up to three times a day as required

Filgrastim daily injection from day 7 for 7 days (see below)

Filgrastim dose:

For patients under 70kg: 30MU (300 micrograms) subcutaneous injection daily

For patients 70kg and above: 48MU (480 micrograms) subcutaneous injection daily

Extravasation risk:

Paclitaxel - vesicant

Cisplatin

Ifosfamide

Interactions

Antiepileptics (CYP 3A4 inducers)

Phenytoin, carbamezapine and phenobarbital increase the clearance of paclitaxel and increase its maximum tolerated dose.

Ciclosporin

Levels of paclitaxel increased after oral administration of ciclosporin.

Fluconazole/Ketoconazole (CYP3A4 inhibitors)

Paclitaxel levels may be increased

Quinine and Verpamil

Paclitaxel levels possibly increased.

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Ondansetron 30 mins before chemotherapy	16mg	PO	
1	Dexamethasone 30 mins before chemotherapy	20mg	IV	
1	Chlorphenamine 30 mins before chemotherapy	10mg	IV	
1	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy (can be discontinued after three cycles for those patients who do not experience a drug hypersensitivity reaction).
1	**Paclitaxel**	**175mg/m^2**	IV	In 500mL sodium chloride 0.9% over 3 hours
1	**Mesna**	**1000mg/m^2**	IV	In 500mL sodium chloride 0.9% over 60 minutes
1	**Cisplatin**	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 90 minutes

1	**Ifosfamide + Mesna**	**500mg/m^2 + 500mg/m^2**	IV	In 1000mL sodium chloride 0.9% with 40mmoL potassium over 8 hours
1	**Ifosfamide + Mesna**	**500mg/m^2 + 500mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 8 hours
2,3, 4 and 5	Ondansetron 30 mins before chemotherapy	16mg	PO	
	Dexamethasone 30 mins before chemotherapy	8mg	PO	
	Cisplatin	**20mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 90 minutes
	Ifosfamide + Mesna	**500mg/m^2 + 500mg/m^2**	IV	In 1000mL sodium chloride 0.9% with 40mmoL potassium over 8 hours
	Ifosfamide + Mesna	**500mg/m^2 + 500mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 8 hours
6	**Mesna**	**2000mg/m^2**	IV	In 1000mL sodium chloride 0.9% over 4 hours
7	**Filgrastim**	300 or 480 micrograms	SC	Daily for 7 days

Cycle is repeated every 21 days for 4 cycles

- Review patient's fluid intake over the previous 24 hours
- Review common toxicity criteria and performance status
- Calculate creatinine clearance using Cockroft and Gault equation (see investigation section)
- Weigh the patient prior to commencing intravenous fluids
- Commence strict fluid balance (input and output)
- Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.
- Paclitaxel in solution may show haziness which is attributed to the formulation of paclitaxel.
- Excessive shaking, agitation, or vibration of paclitaxel may induce precipitation and should be avoided
- Premedication treatment of chlorphenamine, dexamethasone and famotidine is given prior to paclitaxel to reduce the risk of hypersensitivity. Paclitaxel reactions commonly occur within the first few minutes of starting the infusion most likely with

the first two cycles. Carboplatin risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy.

- Famotidine can be stopped after three cycles for those patients who do not experience a drug hypersensitivity reaction.

Hypersensitivity

As with all paclitaxel based chemotherapy, patients may experience allergic reaction during administration. The infusion should be stopped and the following should be administered.

- Hydrocortisone 100 to 200mg IV
- Chlorphenamine 10 mg IV

Refer to the Trusts Hypersensitivity Guidelines for further information.

It should be strongly noted that patients who have severe reactions should not be re-challenged

Ifosfamide

Ensure adequate hydration and that fluids with Mesna are prescribed and administered.
Record patients weight at the same time each day as well as a strict fluid balance chart.
If there is a positive fluid balance of 2 litres or more, weight gain of > 2kg or symptoms of fluid overload give furosemide 20mg orally.

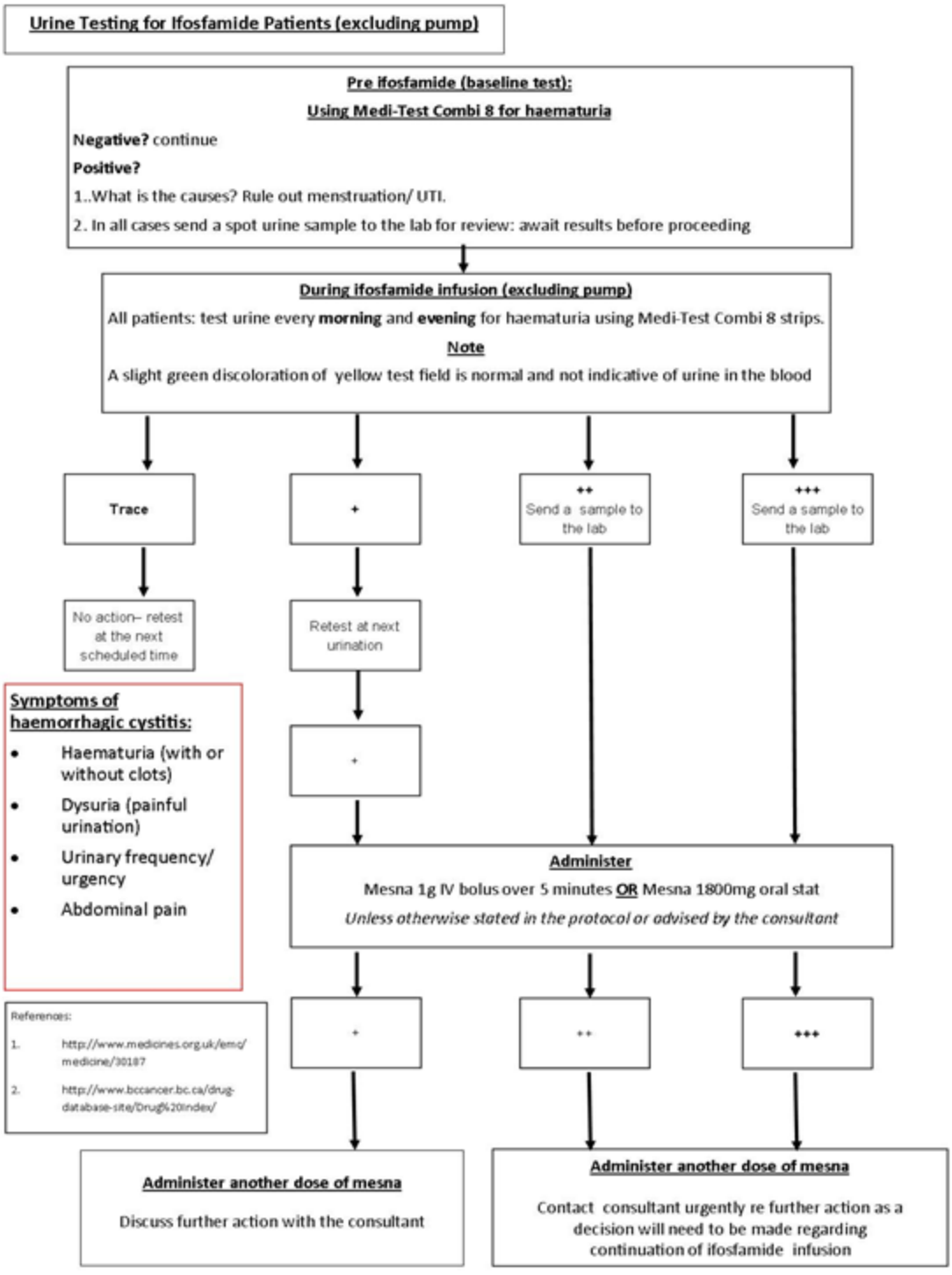
Test urine for microscopic haematuria each cycle (see algorithm)
Observe for insidious signs of encephalopathy, initially somnolence and confusion (see toxicity management)

Main Toxicities:

Haematological	Neutropenia, anaemia, thrombocytopenia,
Cardiac and Vascular disorders	Risk of bradycardia and hypotension is common
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
Musculoskeletal	Arthralgia, myalgia
Nervous system	Paclitaxel and cisplatin: peripheral neuropathy is very common Central neurotoxicity can occur with ifosfamide
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.
Skin and subcutaneous tissue disorders	Alopecia Allergic skin rash frequently associated with pruritus
Ototoxicity	Ototoxicity is common with cisplatin and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000Hz). Decreased ability to hear conversational tones may occur occasionally.
General disorders and administration site conditions	Haemorrhagic cystitis leading to bladder failure with ifosfamide Malaise, fever, chills, urticaria, flu-like syndrome, rash, pruritus. Dehydration, hypokalaemia, hypophosphataemia, hypocalcaemia, tetany, muscle spasms Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)

Investigations:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Comments
Medical Assessment	X		X		X	Alternate cycles
Nursing Assessment		X	X	X	X	
FBC		X	X	X	X	
U&E & LFT		X	X	X	X	Check electrolytes regularly throughout treatment
Serum Creatinine	X	X	X	X	X	
CrCl (Cockroft and Gault)		X	X	X	X	
Ca2+, Mg2+		X	X	X	X	Repeat within the cycle if needed
LDH	X		X	X	X	
AFP, βHCG	X		X	X	X	
CT scan	X					At end of treatment
Informed Consent	X					
Blood pressure measurement	X	X	X	X	X	
PS recorded	X	X	X	X	X	Every administration
Toxicities documented		X	X	X	X	Every administration
Weight recorded	X	X		X	X	Every cycle


Urine Testing for Ifosfamide Patients (excluding pump)
Pre ifosfamide (baseline test):
Using Medi-Test Combi 8 for haematuria
Negative? continue
Positive?
1..What is the causes? Rule out menstruation/ UTI.
2. In all cases send a spot urine sample to the lab for review: await results before proceeding
During ifosfamide infusion (excluding pump)
All patients: test urine every morning and evening for haematuria using Medi-Test Combi 8 strips.
Note
A slight green discoloration of yellow test field is normal and not indicative of urine in the blood
Trace
+
++
Send a sample to the lab
+++
Send a sample to the lab
No action– retest at the next scheduled time
Retest at next urination
+
Symptoms of haemorrhagic cystitis:
Haematuria (with or without clots)
Dysuria (painful urination)
Urinary frequency/ urgency
Abdominal pain
Administer
Mesna 1g IV bolus over 5 minutes OR Mesna 1800mg oral stat
Unless otherwise stated in the protocol or advised by the consultant
References:
1. http://www.medicines.org.uk/emc/medicine/30187
2. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/
+
++
+++
Administer another dose of mesna
Discuss further action with the consultant
Administer another dose of mesna
Contact consultant urgently re further action as a decision will need to be made regarding continuation of ifosfamide infusion

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

Platelets ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if:-

Platelets ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

For subsequent delays, consider increasing course length of filgrastim or dose reduction

Non-haematological toxicity

Renal

Measure serum creatinine each cycle and calculate CrCl using Cockroft and Gault

GFR (mL/min)	Ifosfamide dose
Above 60	100%
40 to 59	70%
Below 40	Clinical decision

GFR (mL/min)	Cisplatin dose
Above 60	100%
45 to 60	70%
Below 45	No further cisplatin, consider carboplatin

Hepatic

Ifosfamide – note that ifosfamide is generally not recommended if bilirubin > ULN or ALP > 2.5 ULN – discuss with consultant if this is the case. Note that in the reference trial patients were eligible for full dose treatment if bilirubin < 30micromol/L.[1]

Paclitaxel

Bilirubin (micromol/L)	Dose
< 26	100%
27 to 51	75%
> 51	50%

Mucositis

Grade 3 or 4 – defer treatment until recovery, reduce subsequent doses by 20%

Neurotoxicity	**Central** Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass. Note that most mild cases of encephalopathy will resolve spontaneously in 24 to 72 hours. If CTC grade 3 or 4 central neurotoxicity occurs (somnolence 30% of the time, disorientation / hallucination / coma or seizures on which consciousness is altered etc) **Stop Ifosfamide infusion** consider the use of methylene blue (methylonium) 50mg IV infusion as follows: 50mg (5ml ampoule of 1% solution) every 4 hours, by IV slow bolus Patients who have had an episode of ifosfamide enduced encephalopathy in a previous cycle should be treated as follows: Give one dose of 50mg (5ml ampoule of 1% solution) IV slow bolus 24 hours prior to ifosfamide. During ifosfamide infusion give 50mg (5ml ampoule of 1% solution) IV slow bolus every 6 hours during the infusion. If repeated grade 3 or 4 central neurotoxicity occurs consider withholding ifosfamide and substitute cyclophosphamide 1500mg/m^2 on d1 only **Peripheral** Both cisplatin and paclitaxel can lead to severe peripheral neuropathy For grade 2 toxicity defer until resolved to grade 1 and consider dose reduction if recurs or at grade 3.

References:

Paclitaxel, ifosfamide and cisplatin efficacy for 1st line intermediate or poor risk germ cell

Feldman et al JCO 2016 34(21):2478-2484

Combination of paclitaxel, ifosfamide and cisplatin is effective 2nd line therapy

Kondagunta et al JCO 2005 23(27): 6549-6555

Paclitaxel, ifosfamide and cisplatin as salvage and consolidation

Kurobe M et al, J Cancer Res Clin Oncol 2015 141:127-133