# VIP (Etoposide, Ifosfamide and Cisplatin)

## Indication

First line treatment for metastatic seminoma, non seminoma or combined tumours where bleomycin is contra-indicated. Usually used for patients with intermediate or poor prognosis disease.

## ICD-10 codes

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

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 – 5 | Etoposide | 75mg/$m^2$ | IV infusion |
| 1 – 5 | Cisplatin | 20mg/$m^2$ | IV infusion |
| 1 | Mesna | 240mg/$m^2$ | IV bolus |
| 1 – 5 | Ifosfamide and mesna | 1.2g/$m^2$ and 600mg/$m^2$ | IV infusion |
| 1 – 5 | Mesna | 600mg/$m^2$ | IV infusion |

## Cycle frequency

21 days

## Number of cycles

Usual maximum of 4 cycles.

## Administration

Etoposide is administered in 1000mL sodium chloride 0.9% over 60 minutes.

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%<br>**OR**<br>Mannitol 10% | 200mL<br><br>400mL | 30 minutes<br><br>30 minutes |
| ***Ensure urine output > 100mL / hour prior to giving cisplatin.***<br>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 600mg/m2 in 500mL sodium chloride 0.9% administered as an IV infusion over 8 hours.

## Pre-medication

Nil

## 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.

## Extravasation

Cisplatin is an exfoliant (Group 4)
Etoposide is an irritant (Group 3)
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 |
| AST/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 etoposide and ifosfamide to 75% dose. 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 arranged if CrCl falls below this value. Discuss with consultant about modifying dose of cisplatin or substituting with carboplatin.

| **CrCl** (mL/min) | **Etoposide dose** |
|---|---|
| >50 | 100% |
| 15-50 | 75% |
| <15 | 50% |

- **Hepatic impairment**

| **Bilirubin** (x ULN) | | **AST/ALT** (x ULN) | **Etoposide 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**

**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. The ifosfamide infusion but be stopped immediately. Severe cases may require methylene blue IV 50mg 6 times a day or PO 50mg four times a day until symptoms resolve.

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

- **Serious side effects**

Myelosuppression
Nephrotoxicity
Ototoxicity
Neurotoxicity
Encephalopathy
Haemorrhagic cystitis
Infertility
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

## 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**

**Phenylbutazone, sodium salicylate and salicylic acid:** may displace etoposide from plasma protein binding thereby increasing systemic exposure.

## Additional comments

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

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## References


- Summary of Product Characteristics Cisplatin (Hospira) accessed 9 December 2015 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Hospira) accessed 9 December 2015 via www.medicines.org.uk
- Summary of Product Characteristics Ifosfamide (Baxter) accessed 9 December 2015 via www.medicines.org.uk
- Nichols CR, Catalano PJ, Crawford D et al. Randomised comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumours: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B study. Journal of Clinical Oncology 1998, 16; 1287-1293


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