EP 500 (Etoposide and Cisplatin)

Indication

Metastatic seminoma or non seminoma where bleomycin is contra-indicated. For intermediate or poor prognosis disease consider VIP as an alternative.

ICD-10 codes

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

Regimen details

EP 500 3 days

Day	Drug	Dose	Route
1 and 2	Cisplatin	50mg/m^2	IV infusion
1, 2 and 3	Etoposide	167 mg/m^2	IV infusion

OR

EP 500 5 days

Day	Drug	Dose	Route
1 – 5	Cisplatin	20mg/m^2	IV infusion
1 – 5	Etoposide	100 mg/m^2	IV infusion

Cycle frequency

21 days

Number of cycles

Maximum of 4 cycles

Administration

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.

Etoposide is administered in 1000-2000mL sodium chloride 0.9% (concentration dependent) and infused over a minimum of 1 hour.

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 4 (3 day regime) or day 6 (5 day regime).

Extravasation

Cisplatin is an exfoliant (Group 4)
Etoposide is an irritant (Group 3)

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

Consider formal EDTA measurement of creatinine clearance in patients with a low body surface area or calculated CrCl $\leq$ 60ml/min renal function

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)
CXR	7 days

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	< 1.5 x ULN
AST/ALT	< 2.5 x ULN

*Prior to day 1 only

If on day 1 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 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)	**Cisplatin dose**
>60	100%
51 – 60	75%
40 – 50	50%
<40	Discuss with consultant – consider carboplatin

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

- **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.

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

- **Serious side effects**

Myelosuppression
Nephrotoxicity
Ototoxicity
Neurotoxicity

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.

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed 29 July 2015 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Hospira) accessed 29 July 2015 via www.medicines.org.uk
- Horwich A, et al. A Medical Research Council randomized trial of single agent carboplatin versus etoposide and cisplatin for advanced metastatic seminoma. Br. J. Cancer 83: 1623-29, 2000
- Kondagunta, GV et al; Etoposide and Cisplatin Chemotherapy for Metastatic Good-Risk Germ Cell Tumors JCO (2005); 23: 9290-9294.

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