Cisplatin and Etoposide (thymic tumours)

Indication
Advanced thymoma or thymic carcinoma.

ICD-10 codes
Codes pre-fixed with C37

Regimen details

Day	Drug	Dose	Route
1	Cisplatin	60mg/m²	IV infusion
1, 2 and 3	Etoposide	120mg/m²	IV infusion

Cycle frequency
21 days

Number of cycles
Up to 8 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. Give a single dose of furosemide 20mg iv if necessary.		
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 low magnesium or low potassium 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 1000mL sodium chloride 0.9% and infused over a minimum of 1 hour.

Pre-medication
Antiemetics as per local guidelines.

Emetogenicity

This regimen has moderate-severe emetic potential.

Additional supportive medication

If magnesium levels < normal reference range refer to local magnesium replacement guidelines.
Consider prophylactic ciprofloxacin 250mg BD and fluconazole 50mg OD for 7 days, starting on day 7, for patients with poor performance status or age >70 years.

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

Baseline radiology CXR and CT scan of chest and upper abdomen.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days

CXR or CT scan every 2 cycles.

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophils	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Creatinine clearance	> 60mL/min
Bilirubin	≤1.5 x ULN
ALT/AST	≤1.5 x ULN
Alkaline phosphatase	≤2.5 x ULN

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)		**Dose modification**
≥ 1.5	and	≥ 100		100%
< 1.5	or	< 100	1st occurrence	Delay treatment until recovery Resume with 100% dose and consider GCSF support
			Subsequent occurrences	Reduce doses as below
Febrile neutropenia or treatment delay for grade 4 neutropenia > 7 days	or	Grade 4 platelets requiring medical intervention or ≥ grade 2 bleeding with thrombocytopenia*	1st occurrence	100% dose and GCSF support or 80% dose
			2nd occurrence	70% dose
			3rd occurrence	Discontinue treatment

* Dose reductions rather than GCSF support would usually be required.

- **Renal impairment**

CrCl (mL/min)	**Cisplatin dose**	**Etoposide dose**
>60	100%	100%
51-60	75%	100%
40-50	50% or switch to carboplatin AUC 5	75%
16-39	Contraindicated	75%
<15	Contraindicated	50%

Carboplatin is contraindicated if CrCl <20mL/min

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**
<1.5	and	< 1.5	100%
1.5-3.0	or	< 1.5-3.0	50%
>3.0	or	> 5	25% or omit (consultant decision)

No dose modification required for cisplatin.

- **Other toxicities**

If grade 3-4 neurotoxicity discontinue cisplatin.

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

- **Serious side effects**

Myelosuppression
Neurotoxicity
Nephrotoxicity

- **Frequently occurring side effects**

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

- **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: can affect protein binding of etoposide.

Additional comments

Consider prophylactic cranial irradiation after completion of chemotherapy.

Hypersensitivity reactions may occur due to cisplatin or mannitol.

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed 13 May 2015 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Hospira) accessed 13 May 2015 via www.medicines.org.uk
- Giaccone G, Ardizzoni A, Kirkpatrick A, et al. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol. 1996 Mar;14 (3):814-20.

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