Cisplatin-Etoposide and Radiotherapy

Indication

First-line chemotherapy for use with concomitant radical radiotherapy for early or locally advanced non-small cell carcinoma (NSCLC), who have a good performance status (WHO PS 0-1).

ICD-10 codes

Codes pre-fixed with C34

Regimen details

Day	Drug	Dose	Route
1 to 5	Etoposide	50mg/m^2/day	IV infusion
1 and 8	Cisplatin	50mg/m^2/day	IV infusion

Cycle frequency

28 days

Number of cycles

2 cycles concurrent with radiotherapy (5 days/week, 30-33 fractions over 6-6.5 weeks)

Administration

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

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%	200mL	10 minutes
OR		
Mannitol 10%	400mL	15 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 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.

Pre-medication
Antiemetics as per local guidelines.

Emetogenicity
This regimen has 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/day 35, 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 dose

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days

Investigations – pre subsequent cycles

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

*The above tests are also required within 48 hours of day 8 dose.

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**

		Dose modification
Neutrophils (x 10^9/L)	≥1.5	100%
	0.5 to <1.5	Delay treatment until recovery Resume with 100% dose and consider GCSF support
	<0.5	Delay treatment until recovery and reduce cisplatin **and** etoposide by 25% for subsequent cycles and consider GCSF support
Platelets (x 10^9/L)	≥100	100%
	75 to <100	Delay treatment until recovery Resume with 100% dose and consider GCSF support
	50 to <75	Delay treatment until recovery Resume with 100% dose and consider GCSF support
	<50	Delay treatment until recovery and reduce cisplatin **and** etoposide by 25% for subsequent cycles and consider GCSF support
Febrile neutropenia		Delay treatment until recovery and reduce cisplatin **and** etoposide by 25% for subsequent cycles and consider GCSF support

- **Renal impairment**

CrCl (mL/min)	**Cisplatin dose**	**Etoposide dose**
≥60	100%	100%
50-59	75%	100%
40-49	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	> 3.0	25% or omit (consultant decision)

No dose modification required for cisplatin.

Other toxicities

Toxicity	**Definition**	**Cisplatin dose**	**Etoposide dose**
Neurotoxicity	≤Grade 1	100%	100%
	Grade 2	50%	100%
	Grade 3	Omit (consider switch to carboplatin)	100%
	Grade 4	Discontinue (consider switch to carboplatin)	Discontinue
Mucositis and stomatitis:	≤Grade 2	Delay until recovery; then consider dose reduction (consultant decision)	Delay until recovery; then consider dose reduction (consultant decision)
	≤Grade 3	Delay until recovery; then consider 50% dose reduction, or omit on 2nd occurrence (consultant decision)	Delay until recovery; then consider 50% dose reduction, or omit on 2nd occurrence (consultant decision)

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

- **Serious side effects**

Myelosuppression
Neurotoxicity
Nephrotoxicity
Ototoxicity

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Stomatitis, mucositis
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 alternative method of anticoagulation during treatment.
Aminoglycoside antibiotics (e.g. gentamycin): increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin. Avoid if possible (if prescribed, close monitoring of renal function and antibiotic levels is required)
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs (e.g. amphotericin, contrast dye, frusemide, NSAIDs): increased nephrotoxicity; not recommended, avoid where possible.
Neurotoxic drugs (e.g. vincristine, paclitaxel): increased neurotoxicity; monitor for neuropathy
Ototoxic drugs (e.g. aminoglycosides, frusemide, NSAIDs): increased risk of ototoxicity
Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.
Phenytoin (+ carbamazepine, valproate): cisplatin reduces absorption and efficacy; monitor levels and adjust dose as necessary (or select alternative antiepileptic (e.g. clonazepam, diazepam, lorazepam)).
Phenylbutazone, sodium salicylate and salicylic acid: can affect protein binding of etoposide.
Avoid Glucosamine and Grapefruit juice (decreased efficacy of etoposide)
CYP3A4 and P-gp inhibitors (e.g. amiodarone, macrolides, ciclosporin, antifungals): increased toxicity of etoposide possible due to reduced clearance

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Reference

- Summary of Product Characteristics Cisplatin accessed 29 August 2019 via https://www.medicines.org.uk/
- Summary of Product Characteristics Etoposide accessed 29 August 2019 via https://www.medicines.org.uk/
- Treatment schedule from eviQ - Non small cell lung cancer definitive cisplatin and etoposide chemoradiation – accessed May 2019
- Senan, S et al., PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Non-squamous Non–Small-Cell Lung Cancer. JCO.2015.64.8824.

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