CISplatin (50mg/m^2) and Etoposide (50mg/m^2) and Thoracic Radiotherapy (TRT) -28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Stage III Non Small cell lung cancer (NSCLC)	C34	00456a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

CISplatin is administered on day 1 and day 8 and etoposide is administered on five consecutive days (Days 1-5) of a 28 day cycle for 2 cycles concurrently with radiotherapy unless disease progression or unacceptable toxicity develops.
Radiotherapy usually starts within 24hours of the first day of chemotherapy.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1-5	Etoposide	50mg/m^2	IV Infusion	1000ml 0.9% NaCl over 1 hour	Repeat every 28 days for a total of 2 cycles
2	1, 8	CISplatin	50mg/m^2	IV Infusion	1000ml 0.9% NaCl over 2 hours (Pre and Post hydration therapy required)[a]	Repeat every 28 days for a total of 2 cycles

[a] **Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

- The administration of etoposide in 1000ml 0.9% NaCl over 1 hour as detailed above may be considered as pre-hydration for CISplatin
- Administer CISplatin as described above

Post hydration:

- Administer 10mmol magnesium sulphate ($MgSO_4$) and 20mmol potassium chloride (KCl) in 1000 ml 0.9% NaCl over 2 hours

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required.
The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload. (2,3)

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Suitable candidate for thoracic radiation

EXCLUSIONS:

- Hypersensitivity to etoposide, CISplatin or any of the excipients.
- CISplatin
  - Pre existing neuropathies ≥ grade 2
  - Creatinine clearance < 60 mL/min
  - Significant hearing impairment/tinnitus
- Severe liver impairment (etoposide)
- Pregnancy
- Breast Feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC Day 1 and Day 8
- Renal and liver profile prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Haematological:

Table 1: Dose modification of ETOPOSIDE for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose Etoposide
≥ 1.5	**and**	≥ 100	100%
1-1.49	**or**	75-99	75%
< 1	**or**	< 75	DELAY

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
Etoposide	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST (Units/L)**	**Dose Etoposide**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent dosing should be based on patient tolerance and clinical effect.					
CISplatin	**CrCl (ml/min)**	**Dose of CISplatin**	No dose reduction necessary			
	≥ 60	100%				
	45-59	75%				
	<45	Consider CARBOplatin /Clinical decision				

Non-Haematological Toxicity:

Table 3: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Grade ≥ 2 peripheral neuropathy	Substitute CARBOplatin AUC 5 or 50% reduction of CISplatin dose after recovery to grade ≤ 1; 100% dose of etoposide.
Grade 3 (Other than mucositis or alopecia)	Delay until recovery to Grade 1. Then reduce dose of CISplatin and etoposide to 75%.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin High **(Refer to local policy).**
Etoposide Low **(Refer to local policy).**

PREMEDICATIONS:

Hydration prior and post CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. Avoid aminoglycoside antibiotics.
- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used,

monitor renal function.

- **Ototoxicity and sensory neural damage**: These are associated with CISplatin therapy. They should be assessed by history prior to each cycle.
- **Hypersensitivity:** Hypersensitivity reactions have been reported with etoposide and CISplatin. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concomitant CISplatin therapy is associated with reduced total body clearance of etoposide.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide
- Current drug interaction databases should be consulted for more information

REFERENCES:

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5. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
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7. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Last updated: 11/03/2019. Accessed Nov2019. Available at https://www.hpra.ie/img/uploaded/swedocuments/Final%20approved%20SPC%20PA0822.199.001.pdf
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9. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at:https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	18/12/2017		Prof Maccon Keane
2	08/01/2020	Reviewed. Standardised treatment table	Prof Maccon Keane
3	24/06/2021	Updated hydration protocol for CISplatin	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.