CARBOplatin (AUC 3), 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) in patients not suitable for treatment with CISplatin	C34	00561a	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.

CARBOplatin 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.
Radiotherapy usually starts within 24 hours of first dose of chemotherapy.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1 and 8	CARBOplatin	AUC 3	IV Infusion	250ml glucose 5% over 30 mins	Repeat every 28 days for a total of 2 cycles
2	1,2,3,4,5	Etoposide	50mg/m^2	IV Infusion	500ml 0.9% NaCl over 60 mins	Repeat every 28 days for a total of 2 cycles

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) X GFR ml/min +25

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR** (eGFR) may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered

- Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay*.

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{\text{S} \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Patients unsuitable for treatment with CISplatin based regimens

EXCLUSIONS:

- Hypersensitivity to etoposide, CARBOplatin or any of the excipients.
- Pregnancy or lactation

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Isotope GFR measurement (preferred) or GFR / creatinine clearance estimation

Regular tests:

- FBC weekly prior to treatment
- 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: Recommended 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: Recommended dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
Etoposide	**Cr Cl (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.					
CARBOplatin	***See below**		No dose adjustment necessary			

***Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of < 60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution.
- If GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required on

each cycle based on a serum creatinine obtained within 48 hrs of drug administration.

- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of Adverse events

Table 3: Recommended dose modification schedule based on adverse events

Adverse reactions	Dose modification
Grade ≥3 (Other than mucositis or alopecia)	Delay until recovery to Grade 1. Then reduce dose of CARBOplatin and etoposide to 75%.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CARBOplatin Moderate **(Refer to local policy)**
Etoposide Low (**Refer to local policy)**

PREMEDICATIONS:

None usually required unless patient has experienced a previous hypersensitivity reaction.

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.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.
- **Hypersensitivity:** Hypersensitivity reactions have been reported with etoposide and CARBOplatin.

DRUG INTERACTIONS:

- Avoid concurrent use of CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.
- 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.

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Version	Date	Amendment	Approved By
1	28/06/2019		Dr Sinead Cuffe
2	09/03/2020	Updated infusion volume for CARBOplatin and etoposide administration	Dr Sinead Cuffe
3	22/10/2021	Updated CARBOplatin dose wording to standard wording; Updated baseline tests and renal impairment (re: CARBOplatin).	Prof. Maccon Keane
4	10/10 /2022	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing , renal dysfunction and creatinine value. Updated baseline tests.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.