CARBOplatin and Oral Etoposide Therapy- 21days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Small cell lung cancer (SCLC) extensive disease	C34	00319a	CARBOplatin - Hospital Etoposide - CDS

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 etoposide is administered on three consecutive days (Days 1-3) of a 21day cycle until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 60 min	Every 21 days
1-3	Etoposide	200mg/m^2	PO	N/A	Every 21 days
CARBOplatin is administered prior to etoposide					
The standard oral etoposide dose is approximately twice the effective intravenous etoposide dose i.e.200 mg/m^2(*orally*) = 100 mg/m^2 (*intravenously*). Prediction of oral dosing based on intravenous dose may be unreliable therefore it is recommended to titrate the oral dose to achieve maximal effect and minimise toxicity.					
Etoposide capsules should be taken on an empty stomach Daily doses greater than 200mg should be given as two divided doses.					

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)** can be done by using the Wright formula or using the Cockroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight for Cockroft and Gault may be considered (3).

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

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

S= 1.04 for females and 1.23 for males

ELIGIBILTY:

- Indications as above
- Patients unsuitable for treatment with CISplatin based regimens
- ECOG 0-2 (0-3 in patients < 70)

EXCLUSIONS:

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

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Blood renal and liver profile

Regular tests:

- FBC weekly prior to treatment
- Renal and liver profile before 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 CARBOplatin in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥ 1.5	**and**	≥ 100	100%
< 1.5	**and**	< 100	Delay one week or until recovery
<0.5 for >5 days or neutropenic fever			Consider dose reduction for etoposide

Renal and Hepatic Impairment:

Table 2: Dose modification of CARBOplatin and etoposide in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="3">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td>CARBOplatin</td><td colspan="3">• Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.
• In case of GFR ≤ 20ml/min carboplatin should not be administered at all.
• If Cockroft & Gault or Wright formula are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
• If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockroft & Gault or Wright formulae taking care this does result in a dose reduction</td><td colspan="4">Probably no dose modification required</td></tr>
<tr><td rowspan="4">Etoposide</td><td>Cr Cl (ml/min)</td><td colspan="2">Dose</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td>>50</td><td colspan="2">100%</td><td>26-51</td><td>or</td><td>60-180</td><td>50%</td></tr>
<tr><td>15-50</td><td colspan="2">75%</td><td>>51</td><td>or</td><td>>180</td><td>Clinical decision</td></tr>
<tr><td><15</td><td colspan="2">50%</td><td colspan="4"></td></tr>
<tr><td colspan="7">Subsequent doses should be based on clinical response</td></tr>
</table>

Table 3: Dose modification schedule based on adverse events

Adverse reactions	Recommended 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 High
Etoposide Minimal to Low **(Refer to local policy).**

PREMEDICATIONS: Not usually required unless patient has experienced a previous hypersensitivity

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.
- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **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

DRUG INTERACTIONS:

- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 inhibitors may decrease the clearance of etoposide.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CARBOplatin - L01XA02
Etoposide - L01CB01

REFERENCES:

1. Johnson DH, Ruckdeschel JC, Keller JH, et al. A randomized trial to compare intravenous and oral etoposide in combination with cisplatin for the treatment of small cell lung cancer. Cancer 1991;67(1 Suppl):245-249.
2. Rossi, A., M. Di Maio, P. Chiodini, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 2012; 30(14):1692-1698
3. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol 2009;64:115-122.
4. Carboplatin Summary of Product Characteristics Last updated 10/11/2019. Accessed April 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-032-001_10112019092721.pdf
5. Etoposide Summary of Product Characteristics. Last updated: 24/07/2019. Accessed May 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2239-006-002_24072019111225.pdf
6. NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. 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	03/05/2016		Dr Maccon Keane
2	02/05/2018	Updated with new NCCP regimen template. Updated title, dosing in renal impairment and emetogenic status	Prof Maccon Keane
3	13/05/2020	Reviewed. Update of emetogenic potential.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.