

CARBOplatin AUC 4 and 5-Fluorouracil 600mg/m² with Radiotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally Advanced Squamous Cell Carcinoma of the Head and Neck	C76	00591a	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 5-Fluorouracil is administered on day 1-4 every 21 days for three cycles.

Chemotherapy is only to be administered if concurrent with radiotherapy.

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	CARBOplatin	AUC 4	IV Infusion	500ml glucose 5% over 30min	Every 21 days for three cycles
2	1-4	5-Fluorouracil ^a	600mg/m ² /day	Continuous IV infusion over 4 days (96 hours)	Infusor pump	Every 21 days for three cycles

^aSee dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency

CARBOplatin dose:

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

$$\text{Dose (mg)} = \text{target AUC (mg/ml x min)} \times (\text{GFR ml/min} + 25)$$

- **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 Cockcroft and Gault formula to measure 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

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- where obesity (body mass index [BMI] $\geq 30 \text{ kg/m}^2$) 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

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

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indication as above
- ECOG 0 to 2

EXCLUSIONS:

- Hypersensitivity to CARBOplatin, 5-Fluorouracil or any of the excipients

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- Neutrophil count $<1.5 \times 10^9/L$
- Platelet count $<100 \times 10^9/L$
- Bilirubin $>1.5 \times ULN$
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

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 / Cr Clearance estimation
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, 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:

- Consider a reduced starting dose in patients with identified partial DPD deficiency
 - Initial dose reduction may impact the efficacy of treatment
 - In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Any dose modification should be discussed with a Consultant

Haematological:

Table 1: Dose modification of CARBOplatin and 5-Fluorouracil in haematological toxicity

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	Dose
≥ 1.0	and	≥ 100	100%
0.5-0.99	or	50-99	Delay treatment until recovery
< 0.5	or	< 50	Delay treatment until recovery and consider reducing CARBOplatin and 5-Fluorouracil by 25% for subsequent cycles
Febrile neutropenia			

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Renal and Hepatic Impairment:

Table 2: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment		
CARBOplatin	*See below	No dose modification required		
5-Fluorouracil	Consider dose reduction in severe renal impairment only	Bilirubin	AST	Dose
		<85	<180	100%
		>85	or >180	Contra-indicated
		Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity.		

*Renal dysfunction and CARBOplatin:

- 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 Cockcroft & Gault or Wright formula are used, the dose should be calculated as required 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 Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 3: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Dysphagia or stomatitis	
Grade 0-2	100%
Grade 3	Delay until improvement and proceed at 75-100%
Grade 4	Discontinue
Weight loss from baseline	
≤10%	100%
>10%	75% if hyperalimentation instituted, otherwise discontinue
Palmar-plantar erythrodysesthesia	
Grade 0-2	100%
Grade 3	75%

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CARBOplatin - High (Refer to local policy).

5-Fluorouracil - Low (Refer to local policy).

PREMEDICATIONS: No specific recommendations

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 aggressively.

CARBOplatin

- **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.

5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **DPD deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil.

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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.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimes.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin
- 5- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil metabolising enzyme DPD.
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	18/12/2020		Dr Cliona Grant
2	27/08/2022	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing and creatinine value. Updated baseline tests. Updated dose modification of CARBOplatin in haematological toxicity. Updated emetogenic potential	Dr Cliona Grant
2a	23/11/2023	Formatting changes and grammatical corrections.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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