Carboplatin and Fluorouracil

Indication

Palliative chemotherapy for recurrent or metastatic head and neck squamous cell cancer for patients where cisplatin and / or cetuximab are not appropriate.

Performance status 0-2

ICD-10 codes

Codes prefixed with C00-C13

Regimen details

Day	Drug	Dose	Route
1	Carboplatin	AUC 5	IV infusion
1-4*	Fluorouracil	750mg/m^2/day	Continuous IV infusion

* 4 days of treatment, commencing day 1 and finishing day 5

The carboplatin dose is calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
Creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation. However, for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) a Nuclear Medicine GFR should be performed. CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

Up to 6 cycles

Administration

Carboplatin is administered in 250-500mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of carboplatin and appropriate therapy.

Fluorouracil is administered by continuous infusion via ambulatory pump over 4 days or by IV infusion in 1000mL sodium chloride 0.9% over 22 hours each day for 4 days.

Pre-medication

Nil

Emetogenicity

This regimen has a moderate-high emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
H_2 antagonist or proton-pump inhibitor if required.
Loperamide if required.

Extravasation

Carboplatin is an exfoliant (Group 3).
Fluorouracil is an inflammatant (Group 2).

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days

Baseline EDTA if suspected or significant renal dysfunction.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days

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
Bilirubin	≤ ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Creatinine Clearance (CrCl)	> 30mL/min
Magnesium	> 0.6 mmol/l

Dose modifications

- **Haematological toxicity**

Defer treatment for 1 week if neutrophil count <1.5 x 10^9/L and/or platelets <100 x 10^9/L.

If delayed on two occasions or grade 3 haematological toxicity reduce carboplatin dose to AUC 4 and fluorouracil to 80% for all future cycles.

If grade 4 haematological toxicity discontinue treatment.

- **Renal impairment**

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	EDTA then 100% dose
< 20	Omit

If CrCl falls by more than 10% from the previous cycle then consider a dose reduction.

Reduce fluorouracil dose only in severe renal impairment – discuss with consultant

- **Hepatic impairment**

AST +/or ALT		**Alkaline Phosphatase**	**Fluorouracil dose**
≤ 1.5 x ULN	and	≤ 2.5 x ULN	100%
>1.5 - ≤ 3.5 x ULN	and/or	> 2.5 -≤ 6 x ULN	Start at 80%*
> 3.5 x ULN	and/or	> 6 x ULN	Discuss with consultant. Usually start at 50% if no other toxicity*

*Fluorouracil can be increased if no toxicity.

Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. If bilirubin ≥ 3 x ULN and/or transaminases ≥ 5 x ULN discuss with consultant.

- **Other toxicities**

For non-haematological toxicity (except alopecia) delay treatment until resolved to ≤ grade 1 and discuss with consultant.

Toxicity	**Definition**	**Dose adjustment**	
		Fluorouracil	**Carboplatin**
Diarrhoea	Grade 1 Manage symptomatically with loperamide +/or codeine phosphate	100%	100%
	Grade 2 2nd occurrence	80%	100%
	Grade 3 1st occurrence	80%	100%
	Grade 3: 2nd occurrence	50%	80%
	Grade 4: 1st occurrence	Discontinue treatment	
Stomatitis/Mucositis	Grade 1: Manage symptomatically with mouthwashes	100%	100%
	Grade 2 2nd occurrence	80%	100%
	Grade 3: 1st occurrence	80%	100%
	Grade 3: 2nd occurrence	50%	80%
	Grade 3: 3rd occurrence	Discontinue treatment	
	Grade 4: 1st occurrence	Discontinue treatment	
Hypomagnesaemia	<0.4mmol/l (symptomatic)	IV Magnesium Sulphate 2-4g as per local policy	
	<0.4mmol/l (asymptomatic)	Oral Magnesium salts 8mmol BD-TDS	
	0.4 – 0.6 mmol/l	Supplementation if symptomatic or ongoing risk orally unless contraindicated	
	NB Magnesium salts should be taken with food to minimise diarrhoea.		

Dose reductions for stomatitis or diarrhoea are based on the dose given in the preceding cycle and continue for remaining cycles. If multiple toxicities, the dose administered is based on the most severe toxicity experienced.

If ≥ grade 2 stomatitis or diarrhoea, fluorouracil must not be given. Treatment must be deferred one week until toxicity has resolved to ≤ grade 1 toxicity.

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

- **Serious side effects**

Myelosuppression
Cardiac toxicity
Secondary malignancy
Teratogenicity
Renal impairment
Neurotoxicity
Hypersensitivity reactions

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea or constipation
Stomatitis and mucositis
Peripheral neuropathy
Ototoxicity
Palmar-plantar erythema
Alopecia (mild)

- **Other side effects**

Electrolyte imbalances
Rash
Loss of appetite, taste alterations (metallic)
Fatigue
Sore eyes and runny nose
Oedema
Rare vascular toxicity including coronary vasospasm
Allergic reactions

Significant drug interactions – for full details consult product literature/ reference texts

Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of fluorouracil.
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Sorivudine: Inhibits dihydropyrimidine dehydrogenase – use with caution.
Phenytoin: Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with fluorouracil.
Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Carboplatin:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Avoid use in patients with known DPD deficiency.

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Hypersensitivity reactions may occur due to carboplatin.

References

- Posner MR, Hershock DM, Blajman CR, Michiewicz E; Winquist E, Gorbounova V et al. Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer. N Engl J Med. 2007;257:1705-15
- Summary of Product Characteristics Carboplatin (Hospira) accessed 4 Oct 2017 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 4 Oct 2017 via www.medicines.org.uk

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