Carboplatin and Paclitaxel (oesophagus)

Indication

Neo-adjuvant treatment for resectable cancer of the oesophagus or oesophagogastric junction.
WHO performance status 0-2.

ICD-10 codes

Codes pre-fixed with C15 and C16

Regimen details

Day	Drug	Dose	Route
1, 8, 15, 22, 29	Paclitaxel	50 mg/m²	IV infusion
1, 8, 15, 22, 29	Carboplatin	AUC 2*	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The 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) an EDTA should be performed.
CrCl should be capped at 125mL/min.

Cycle frequency

Weekly for 5 weeks concurrent with radiotherapy. Starting on the first day of radiotherapy.

Number of cycles

As above

Administration

Paclitaxel should be administered first.

Paclitaxel is administered in a 250mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 1 hour. Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Carboplatin should be administered in 250mL glucose 5% over 30 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 paclitaxel or 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 re-started 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 paclitaxel or carboplatin and appropriate therapy initiated.

Pre-medication

30 minutes prior to paclitaxel: chlorphenamine 10mg IV, dexamethasone 8mg IV and ranitidine 50mg IV.
Antiemetics as per local guidelines.

Emetogenicity
Days 1, 8, 15, 22, 29 have moderate emetic potential.

Additional supportive medication
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy

Extravasation
Carboplatin – irritant (Group 3)
Paclitaxel - vesicant (Group5)

Investigations – pre first cycle

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

Baseline EDTA if suspected or significant renal dysfunction.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Pre day 8, 15, 22, 29. Results valid for 72 hours
U+E (including creatinine)	Pre day 8, 15, 22, 29. Results valid for 72 hours
LFTs	Pre day 8, 15, 22, 29. Results valid for 72 hours

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	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Bilirubin	< 5 x ULN
AST/ALT	< 5 x ULN
Creatinine Clearance (CrCl)	> 20 mL/min (and < 20% change)

Dose modifications

- **Haematological toxicity**

If on day 8, 15, 22, 29, and 36 the WBC are < 1.0 × 10^9/L and/or platelets < 50 × 10^9/L, chemotherapy will be delayed by 1 week until recovery above these values.
In case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C) or in case of severe bleeding or requiring ≥ 2 units of platelet transfusions further chemotherapy will be withheld.

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose modification**	
			Carboplatin	**Paclitaxel**
≥ 1.0	and	≥ 50	100%	100%
< 1.0	or	< 50	Delay 1 week	Delay 1 week

- **Renal impairment**

If calculated CrCl falls by >20% from previous dose, consider dose recalculation.

CrCl (mL/min)	**Carboplatin dose**
> 20	100%
≤ 20	Contra-indicated

- **Hepatic impairment**

Paclitaxel should be used with caution and close monitoring in moderate hepatic impairment and is contraindicated in severe hepatic impairment.

- **Other toxicities**

Any Grade 3-4 toxicity (except mucositis and alopecia) – delay until ≤ Grade 1 toxicity and reduce dose. Discuss with consultant.

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

- **Rare or serious side effects**

Myelosuppression
Infertility
Teratogenicity
Neurotoxicity
Hypersensitivity reactions
Pulmonary fibrosis
Electrolyte disturbances
Arrhythmias
Cardiac failure

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue

- **Other side effects**

Elderly patients may have a higher incidence of severe neuropathy, severe myelosuppression, or cardiovascular events compared to younger patients.

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

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Carboplatin only:
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

Radiotherapy is given as follows: 41.4Gy in 23 fractions, 5 days per week.

References

- Summary of Product Characteristics Carboplatin (Hospira) accessed via www.medicines.org.uk (18 June 2014)
- Summary of Product Characteristics Paclitaxel (Hospira) accessed via www.medicines.org.uk (18 June 2014)
- Gaast AV et al, the CROSS Study Group. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study. Accessed online on: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74

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