Carboplatin and Paclitaxel and Radiotherapy

Indication

Chemotherapy for use with concomitant radical radiotherapy for early or locally advanced non-small cell lung carcinoma (NSCLC) in patients unfit for cisplatin and vinorelbine or for those in whom cisplatin is contra-indicated.

WHO performance status 0-1.

ICD-10 codes

Codes pre-fixed with C34

Regimen details

Day	Drug	Dose	Route
1, 8, 15, 22, (29, 36, 42)**	Paclitaxel	45 mg/m²	IV infusion
1, 8, 15, 22, (29, 36, 42)**	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.

**Total number of doses of chemotherapy given depends on radiotherapy:
55Gy in 20# will have 4 doses
60Gy in 30# will have 6 doses
64Gy in 32# will have 7 doses

Cycle frequency

Weekly for 4-7 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. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate therapy initiated.

Pre-medication

The following should be administered 30 minutes prior to paclitaxel:
Chlorphenamine 10mg IV
Dexamethasone 8mg IV
Ranitidine 50mg IV

Antiemetics as per local guidelines.

Emetogenicity

This regimen has 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, 36, 42. Results valid for 24 hours
U+E (including creatinine)	Pre day 8, 15, 22, 29, 36, 42. Results valid for 24 hours
LFTs	Pre day 8, 15, 22, 29, 36, 42. Results valid for 24 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	≥ 1.5 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	See below
AST/ALT	See below
Creatinine Clearance (CrCl)	> 20 mL/min (and < 20% change – see below)

Dose modifications

- **Haematological toxicity**

On day of chemotherapy:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose modification**	
			Carboplatin	**Paclitaxel**
≥ 1.5	and	≥ 75	100%	100%
1.0 - 1.49	and/or	50-74	50%	50%
< 1.0	or	< 50	Omit	Omit

If a dose reduction is required due to low neutrophils or platelets, then that dose reduction is maintained for subsequent cycles.
Patients who omit a dose due to neutrophils < 1.0 x 10^9/L or platelets <50 x 10^9/L may re-start once their FBC is above these levels but with a 50% dose reduction
Further chemo may be omitted at the treating consultant's discretion in cases of neutropenic sepsis or bleeding due to thrombocytopenia.

- **Renal impairment**

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

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

No dose modification required for paclitaxel.

- **Hepatic impairment**

Paclitaxel
Paclitaxel should be used with caution and close monitoring in moderate hepatic impairment and is contraindicated in severe hepatic impairment. Discuss with prescriber/consultant if bilirubin >1.5 x ULN and/or ALT > 2.5 x ULN.

Carboplatin
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**

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

References

- Summary of Product Characteristics Carboplatin (Hospira) accessed via www.medicines.org.uk (20 January 2019)
- Summary of Product Characteristics Paclitaxel (Hospira) accessed via www.medicines.org.uk (20 January 2019)
- Belani et al. Combined Chemoradiotherapy Regimens of Paclitaxel and Carboplatin for Locally Advanced Non–Small-Cell Lung Cancer: A Randomized Phase II Locally Advanced Multi-Modality Protocol. Journal of Clinical Oncology 2005. 23:25, 5883-5891
- Liang et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Annals of Oncology 2017. 28:4, 777–783
- Bradley et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. The Lancet 2015. 16:2, 187-199

Written/reviewed by: Dr G Ayre (Consultant Oncologist, UHBristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: January 2019