Cisplatin/Carboplatin Pemetrexed Osimertinib Protocol

Indication

Untreated, non-squamous EGFR-mutated (exon 19 deletion or L858R mutation) advanced non–small-cell lung cancer (NSCLC)

Regimen details

Osimertinib 80mg once daily orally
Pemetrexed 500mg/m^2 intravenously
Carboplatin AUC5 **or** cisplatin75mg/m^2 intravenously

Cycle frequency

Every 21 days

Number of cycles

Cisplatin/carboplatin is given for 4 cycles. Osimertinib and pemetrexed are given until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment

Administration

Osimertinib

Osimertinib is taken orally daily.
The tablet should be swallowed whole with water and it should not be crushed, split or chewed
It can be taken with or without food at the same time each day
If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50 mL of non-carbonated water. It should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added.
If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15mL for the initial dispersion and 15mL for the residue rinses. The resulting 30mL of liquid should be administered as per the naso-gastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water

Pemetrexed

Pemetrexed should be administered first, followed by carboplatin or cisplatin.
Pemetrexed is given in 100ml 0.9% sodium chloride over 10 minutes.

Carboplatin

Carboplatin is given in 500ml 5% dextrose 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, refer to the alliance protocol for management of hypersensitivity.

Cisplatin

Cisplatin should be given according to the schedule below

Drug	Fluid	Time
Pemetrexed 500mg/m^2	100ml 0.9% sodium chloride	10 minutes
Potassium chloride 20mmol, magnesium sulphate 10mmol	1 litre 0.9% sodium chloride	2 hours
Cisplatin 75mg/m^2	1 litre 0.9% sodium chloride	2 hours
Potassium chloride 20mmol, magnesium sulphate 10mmol	1 litre 0.9% sodium chloride	2 hours

Pre-medication

Folic acid 400µg OD orally beginning 1-2 weeks prior to the first dose of pemetrexed continuing 3 weeks after the last dose of pemetrexed.
Vitamin B12 1000µg IM injection 1-2 weeks prior to the first dose of pemetrexed repeated every 9 weeks until 3 weeks after the last dose of pemetrexed.
Dexamethasone 4mg BD should be taken the day before, the day of and the day after treatment with pemetrexed

Emetogenicity

Highly emetogenic (cisplatin)
Moderately emetogenic (carboplatin)
Pemetrexed given alone has minimal emetogenicity

Additional supportive medication

See above for vitamin supplementation for pemetrexed
Emollient, steroid cream and loperamide should be provided for osimertinib

Extravasation

Cisplatin is an exfoliant
Pemetrexed is an inflammitant
Carboplatin is an irritant

Investigations – pre first cycle

Standard pre-SACT investigations

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), calcium
ECG if clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 50 mL/min (60 ml/min prior to cycle 1) for cisplatin. ≥ 45 mL/min for pemetrexed See under Dose Modifications for adjustment of carboplatin dose
Bilirubin	≤ 1.5 x ULN
AST	<3 x ULN or < 5 x ULN in presence of liver metastases
Alkaline phosphatase	<3 x ULN or < 5 x ULN in presence of liver metastases

Dose modifications

Haematological toxicity

If neutrophils < 1.5 x 10^9/L and platelets < 100 x 10^9/L delay for 1 week. If resolved then continue with 100% dose. If 2 or more delays then reduce doses of cisplatin/carboplatin and pemetrexed to 75%.

Renal impairment

CrCl (ml/min)	Cisplatin dose
≥ 60	100%
50-59	75%
40-49	50% (consider switching to carboplatin AUC 5)
< 40	Contraindicated

Pemetrexed should NOT be administered if CrCl <45 ml/min

Carboplatin dose should be recalculated if the serum creatinine increases by >20% from baseline

Caution with osimertinib in severe renal impairment (CrCl <15ml/min)

Hepatic impairment

Pemetrexed: No information available for patients with bilirubin > 1.5 x ULN and/or AST/ALT > 3 x ULN (5 x ULN if liver metastases present) – consultant decision
Cisplatin/carboplatin: No dose modification required
Osimertinib: do not use in severe hepatic impairment

Mucositis

Grade 3-4: reduce pemetrexed to 50% dose and continue with 100% dose cisplatin/carboplatin.

Neurotoxicity

Grade 2: reduce cisplatin/carboplatin to 50% dose and continue with 100% dose pemetrexed.
Grade 3-4: discontinue cisplatin/carboplatin.

Any other grade 3-4 toxicity

Reduce cisplatin/carboplatin and pemetrexed to 75% of previous dose

Management of osimertinib-related toxicities

Target organ	Adverse effect	Dose modification
Lung	Interstitial Lung disease / Pneumonitis	Permanently discontinue Osimertinib
Heart	QTc interval greater than 500 msec on at least 2 separate ECGs with no signs and symptoms of arrhythmia	Withhold Osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue Osimertinib
Other	Other Grade 3 or higher adverse reaction	Withhold Osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue Osimertinib

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Ototoxicity
Nephrotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea
Oedema
Haematuria
Rash, pruritis

- **Other side effects**

Alopecia
Rash
Fatigue
Nail changes

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.

Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.

Diuretics: increased risk of nephrotoxicity and ototoxicity

Nephrotoxic drugs: increased nephrotoxicity; not recommended

Ototoxic drugs: increased risk of ototoxicity

Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary.

Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided from 5 days before each dose of pemetrexed until 2 days after each dose

CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, St. John's Wort) may decrease efficacy of osimertinib. Avoid co-administration. Concomitant use of St. John’s Wort is contraindicated.

CYP3A4 inhibitors (e.g. itraconazole) may increase plasma levels of osimertinib. Closely monitor for adverse reactions.

Breast Cancer Resistance Protein (BCRP) substrates: osimertinib is a competitive inhibitor of BCRP. If taking BCRP substrates, patients should be closely monitored for tolerability

Additional comments

References

Tagrisso SPC - https://www.medicines.org.uk/emc/product/7615/smpc

Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. Planchard et al N Engl J Med 2023;389:1935-1948

This protocol has been reviewed by Dr Lam consultant oncologist

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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