SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Carboplatin / Etoposide (Oral and IV regimens) Small Cell Carcinoma

PROTOCOL REF: MPHACAETLU
(Version No: 1.1)

Approved for use in

Limited stage small cell lung cancer (SCLC) with radiotherapy (RT) for curative intent, either concurrent to start with second cycle or sequential after the completion of chemotherapy, where **carboplatin is used as an alternative to cisplatin** in patients with a Creatinine Clearance (CrCl) calculated using Cockroft and Gault (C&G) formula < 45 ml/min or in case of deafness. Must fulfill the following criteria:

- Fully staged with CT including brain CT or MRI, with or without PET-CT.
- ECOG performance status (PS) ≤ 2.

Extensive stage SCLC (chemotherapy only).

Small cell cancer of any origin:

- With RT- curative intent
- Without RT- palliative intent for advanced or metastatic disease

Dosage

Drug	Dose	Route	Frequency
Carboplatin	**AUC 5**	IV infusion	Day 1 only
Etoposide phosphate OR	**100mg/m^2**	IV infusion	

Etoposide			
Etoposide*	**200mg/m^2**	PO in 2 divided doses	Days 2 & 3
OR			
Etoposide* (as standard etoposide or etoposide phosphate)	**100mg/m^2**	IV Infusion	Days 2 & 3

Repeated every 3 weeks for up to 4 cycles

Etoposide

Etoposide is available as two formulations standard etoposide or etoposide phosphate. There has been a longstanding supply problem with etoposide phosphate therefore the formulation currently in use at CCC is standard etoposide. However, the following protocol outlines administration for both formulations in case etoposide phosphate becomes available in the future as this has better stability.

Days 2 and 3 can be given orally but oral absorption is variable in comparison to the IV route (100 mg oral dose would be comparable to a 75 mg intravenous dose; a 400 mg oral dose would be comparable to a 200 mg intravenous dose).

Carboplatin

Meditech calculates creatinine clearance/GFR using the Wright formula (application for using Wright formula is available on the Remote Citrix Web Portal). Please refer to 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment.

Calvert formula for Carboplatin dosage-:

Carboplatin dose in mg = AUC x (GFR or CrCl + 25)

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged.

Counselling Points

If having concurrent chemo-radiotherapy (CRT) then RT to start with cycle 2 of chemotherapy.

Oral etoposide is available as 50mg or 100mg soft capsules. Unless there is a supply shortage of 50mg strength capsules, dose will be rounded to the nearest 50mg capsule and supplied in this strength. To be swallowed whole on an empty stomach (one hour before or 2 hours after food).

Please contact the triage line if any of the following symptoms occur:

- Easy bruising or bleeding.
- Uncontrolled nausea, vomiting, constipation or diarrhoea.
- Severe jaw pain or headache.
- Redness, swelling, pain or sores where the needle was place or along the arm.
- Redness, swelling, pain or sores on your lips, tongue, mouth or throat.
- Skin rash or itching.

- Ringing in your ears or hearing problems.
- Numbness or tingling in feet or hands or painful leg cramps.
- Signs of anaemia such as unusual tiredness, shortness of breath or weakness.

Emetogenic risk:

Moderately emetogenic.

Supportive Treatments:

Dexamethasone orally 4mg twice daily for 3 days

Metoclopramide 10mg orally up to 3 times a day as required. Administration for a maximum of 5 consecutive days.

Aprepitant 125mg orally 1 hour before treatment on day 1 then 80mg once a day 1 hour before treatment on days 2 and 3 (2nd line anti-emetic).

Filgrastim to be supplied as primary prophylaxis when SACT given for curative intent - subcutaneous injection daily for 7 days starting on day 5, dose as follows:

- Weight < 70kg- Filgrastim 300 micrograms daily SC.
- Weight ≥ 70kg- Filgrastim 480 micrograms daily SC.

Interactions

Aminoglycosides e.g. gentamicin, vancomycin and diuretics

Increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests carried out as indicated.

Phenytoin- Carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

Co-administration of antiepileptic drugs and etoposide can lead to decreased seizure control

Warfarin

The effects of warfarin may be increased. Monitor INR closely.

Extravasation risk

Carboplatin: Irritant

Etoposide (as standard etoposide or etoposide phosphate): Irritant

Refer to the CCC policy for 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	Carboplatin	Patients with creatinine clearance values of less than 60 mL/min are at greater risk to develop myelosuppression. The optimal use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function. Carboplatin is contraindicated if GFR or CrCl ≤ 20 ml/min. Do not give carboplatin and discuss with clinical team.
	Etoposide	GFR > 50 ml/min: no dose adjustment is needed GFR 10-50 ml/min: 75% of the original dose, increase if tolerated Haemodialysis: not dialysed, consider 75% of the original dose

Hepatic	Carboplatin	No need for dose adjustment is required.
	Etoposide	Bilirubin < 50 micromol/L and normal albumin and normal renal function: no need for dose adjustment is expected

		Bilirubin ≥ 50 micromol/L or decreased albumin levels: consider 50% of the dose, increase if tolerated

Administration

Cycles 1 to 4 every 21 days

Oral etoposide on days 2 and 3

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Carboplatin	**AUC 5**	IV	In 500mL glucose 5% over 30 to 60 minutes
	Etoposide phosphate	**100mg/m^2**	IV	In 100mL sodium chloride 0.9% infusion over 15 minutes
2	**Etoposide capsules**	**200mg/m^2**	PO	in 2 divided doses
3	**Etoposide capsules**	**200mg/m^2**	PO	in 2 divided doses

OR

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Carboplatin	**AUC 5**	IV	In 500mL glucose 5% over 30 to 60 minutes
	Etoposide	**100mg/m^2**	IV	In 250mL to 1000ml sodium chloride 0.9% infusion over 60 minutes
2	**Etoposide capsules**	**200mg/m^2**	PO	in 2 divided doses

3	**Etoposide capsules**	**200mg/m^2**	PO	in 2 divided doses

ALTERNATIVELY

Cycles 1 to 4 every 21 days

IV etoposide on days 2 and 3

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Carboplatin	**AUC 5**	IV	In 500mL glucose 5% over 30 to 60 minutes
	Etoposide phosphate	**100mg/m^2**	IV	In 100mL sodium chloride 0.9% infusion over 15 minutes
2	**Etoposide phosphate**	**100mg/m^2**	IV	In 100mL sodium chloride 0.9% infusion over 15 minutes
3	**Etoposide phosphate**	**100mg/m^2**	IV	In 100mL sodium chloride 0.9% infusion over 15 minutes

OR

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	8mg	PO	30 minutes before chemotherapy
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	Etoposide	**100mg/m^2**	IV	In 250mL to 1000ml sodium chloride 0.9% infusion over 60 minutes

2	**Etoposide**	**100mg/m^2**	IV	In 250mL to 1000ml sodium chloride 0.9% infusion over 60 minutes
3	**Etoposide**	**100mg/m^2**	IV	In 250mL to 1000ml sodium chloride 0.9% infusion over 60 minutes

Concurrent CRT:

- **Patients will have ONCE daily RT treatment schedule.** Refer to table below for the relevant RT treatment schedule, outlining corresponding day of treatment and fraction of radiotherapy.
- **Treatment should commence on a Monday afternoon to coincide with the first day of RT (from cycle 2)** and to allow for the etoposide to be made in the morning by cytopharmacy as it has a short expiry. SACT DOES NOT NEED to be administered within a specific timeframe in relation to the RT fraction, PROVIDED it commences on the day RT starts.
- **If start date is for a cycle is delayed until Tuesday then day 1 of next cycle should be moved to commence the subsequent cycle on Monday** i.e. cycle shortened to 20 instead of 21 days.
- **Delays in the administration of the second cycle of chemotherapy should not delay the start of radiotherapy.**

40Gy/15#/19 days – ONCE daily RT (patients felt not suitable for a twice daily schedule)

Treatment Day	Radiotherapy Fraction	Week day	Chemotherapy	Chemotherapy
1	1	MO	Etoposide	Carboplatin
2	2	TU	Etoposide	
3	3	WE	Etoposide	
4	4	TH		
5	5	FR		

6		SA		
7		SU		
8	6	MO		
9	7	TU		
10	8	WE		
11	9	TH		
12	10	FR		
13		SA		
14		SU		
15	11	MO		
16	12	TU		
17	13	WE		
18	14	TH		
19	15	FR		

Main Toxicities

Gastrointestinal	Nausea, vomiting, diarrhoea, abdominal pain,anorexia constipation, mucositis (including stomatitis and oesophagitis)
General disorders	Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) Renal function impairment Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol. Malaise, urticaria. flu-like syndrome, rash, pruritus, alopecia
Haematological	Neutropenia, anaemia, thrombocytopenia Myelosuppression may be more severe and prolonged in patients with impaired renal function, extensive prior treatment, poor performance status and age above 65.
Vascular	Etoposide can cause hypertension, transient systolic hypotension following rapid intravenous administration.

Hepatobiliary	Abnormalities of liver function tests (usually mild to moderate).The alkaline phosphatase (ALP) level is increased more frequently than transaminases or total bilirubin. The majority of these abnormalities regress spontaneously during treatment.
Hypersensitivity reactions	Skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus Risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy
Nervous system	Paraesthesia and decreased deep tendon reflexes.
Ototoxicity	Carboplatin- tinnitus and hearing loss

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	x					
Clinical Assessment	x		x		x	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	x	x	x	x	x	Every cycle
FBC	x	x	x	x	x	Every cycle
U&E & LFTs & Magnesium	x	x	x	x	x	Every cycle
Calculate GFR check carboplatin dose using the carboplatin calculator*	x	x	x	x	x	Every cycle
CT scan	x				x	Every 3 months or if clinically indicated

ECG						If clinically indicated
Full observations *(BP, HR, RR, O2 sats)*		x	x	x	x	Every cycle
Weight recorded	x	x	x	x	x	Every cycle
Height	x					

* Please refer to:

- 'Dosage' section for full details on carboplatin dosing.
- 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment. For patients having concurrent CRT, if carboplatin dose is to be changed then day 1 of treatment should ONLY be deferred by 1 day to allow SACT to continue to be aligned with RT.

Dose Modifications and Toxicity Management

Haematological Toxicity

Proceed on day 1 (FBC ONLY required prior to day 1- do not repeat on days 2 to 3) if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non Haematological Toxicity

Infusion related reactions	These can occur with carboplatin and rarely with etoposide. Hypotension can occur if etoposide is administered too quickly – slower the infusion and give subsequent infusions at the slower rate Hypertension and flushing can also occur – stop infusion, monitor; blood pressure usually reverts to normal after a few hours

References

1. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18(8):1116-1125. doi:10.1016/S1470-2045(17)30318-2
2. Radiotherapy for lung cancer RCR consensus statements. Accessed July 21, 2022. Accessed via www.rcr.ac.uk
3. SmPC for Carboplatin 10 mg/ml Intravenous Infusion, Hospira – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated June 2020)
4. SmPC for ETOPOPHOS 100mg Powder for Solution for Injection, Neon Healthcare Ltd – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated February 2022)
5. SmPC for Etoposide 20 mg/ml Concentrate for Solution for Infusion, Accord Helathcare Ltd – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated April 2019)
6. SmPC for VEPESID 100 mg soft capsule, soft, Neon Healthcare Ltd – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated january 2021)
7. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

8. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340(4):265-271.

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
October 2017	1.0	Tara Callagy Lung SRG Pharmacist	New regimen protocol
August 2022	1.1	Hala Ghoz Lung SRG Pharmacist	Amendments made in line with new SCLC CRT protocol