SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Dose Fractionated Cisplatin / Etoposide Concurrent with TWICE Radiotherapy (RT) Limited Stage SCLC

PROTOCOL REF: MPHADFCEC
(Version No: 1.0)

Approved for use in

First line treatment:

- **Limited stage small cell lung cancer (SCLC)** with radiotherapy (RT) for curative intent, **administered concurrently to start with second cycle of chemotherapy** and fulfills the following criteria:
    - Fully staged with CT including brain CT or MRI, with or without PET-CT.
    - ECOG performance status (PS) ≤ 2.
    - Serum creatinine level < 130 micromol/L (µmol/L) at baseline.

NOTE: For ONCE daily concurrent/sequential RT regimen please refer to separate protocol 'Cisplatin / Etoposide Concurrent or Sequential with ONCE Daily Radiotherapy (RT) Limited Stage SCLC'.

Dosage

Concurrent chemo-radiotherapy (CRT) - RT to start with cycle 2 of SACT

Drug	Dose	Route	Frequency
Cisplatin	**25mg/m^2**	IV infusion	Days 1 to 3
Etoposide (as standard etoposide or etoposide phosphate)	**100mg/m^2**	IV Infusion	

Repeated every 21 days for 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.

Cisplatin

Check renal function before commencing cisplatin using Cockcroft and Gault Creatinine Clearance (CrCl) equation:

Calculate creatinine clearance using Cockcroft and Gault equation:

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

CrCl must be ≥45 mL/min for cisplatin based treatment. Please ensure the dose has been adjusted if renal function is between 45 and 60 ml/min.

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.

Confirm patient understanding of the need to **ensure good oral fluid intake** while on SACT to aid the clearance of cisplatin and therefore minimise toxicities. Recommended fluid intake of 2 litres in the 24 hours following chemotherapy (caffeinated drinks are not counted, recommend decaffeinated alternatives).

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:

Highly 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.

Filgrastim to be supplied as primary prophylaxis- 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

This list is not exhaustive Please consult SmPC for each agent full list of interactions.

Cephalosporins, amphotericin B, contrast media, loop diuretic (furosemide or bumetanide) or aminoglycosides (gentamicin, vancomycin)

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

Concomitant phenytoin with:

Cisplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages. Monitor the levels of phenytoin in plasma, and adjust the dose accordingly.

Etoposide is associated with increased etoposide clearance and reduced efficacy.

Co-administration of enzyme-inducing antiepileptic drugs and etoposide can lead to decreased seizure control and increased etoposide clearance

Weakened live vaccines

Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease. In view of the risk of generalised illness, it is advisable to use an inactive vaccine if available.

Warfarin

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

Extravasation risk

Cisplatin: 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:

<table>
<tr><td rowspan="2">Renal</td><td>Cisplatin</td><td>Calculate renal function using Cockcroft and Gault. If borderline, a nuclear GFR/DTPA is recommended.

<table>
<tr><th colspan="2">Cisplatin</th></tr>
<tr><th>CrCl (mL/min)</th><th>Dose</th></tr>
<tr><td>≥ 60 mL/min</td><td>Give 100%</td></tr>
<tr><td>45 to 59 ml/min</td><td>Give 75%
Day 1- proceed with 25mg/m^2
Day 2 & 3- reduce to 15mg/m^2</td></tr>
<tr><td>< 45 mL/min</td><td>Contraindicated</td></tr>
</table></td></tr>
<tr><td>Etoposide</td><td>GFR > 50 ml/min: no dose adjustment is needed
GFR 10-50 ml/min: 75% of the original dose, increase if tolerated</td></tr>
</table>

		Haemodialysis: not dialysed, consider 75% of the original dose

Hepatic	Cisplatin	No need for dose adjustment is required.
	Etoposide	Bilirubin < 50 µmol/L and normal albumin and normal renal function: no need for dose adjustment is expected Bilirubin ≥ 50 µmol/L or decreased albumin levels: consider 50% of the dose, increase if tolerated

Administration

Cycles 1 to 4 repeated every 21 days

Standard Etoposide Formulation

Day	Drug	Dose	Route	Diluent and rate
1 to 3	**Dexamethasone**	8mg	oral	30 minutes before chemotherapy
	Ondansetron	16mg	oral	30 minutes before chemotherapy
	Etoposide*	**100mg/m^2**	IV	In 1000ml sodium chloride 0.9% infusion over 60 minutes
	Cisplatin	25mg/m^2	IV Infusion	In 500mL sodium chloride 0.9% over 60 minutes
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes

* Etoposide in 1000ml sodium chloride 0.9% is the pre-hydration.

OR

Etoposide Phosphate Formulation

Day	Drug	Dose	Route	Diluent and rate
1 to 3	**Dexamethasone**	8mg	oral	30 minutes before chemotherapy

	Ondansetron	16mg	oral	30 minutes before chemotherapy
	Etoposide phosphate	**100mg/m^2**	IV	In 100mL sodium chloride 0.9% infusion over 15 minutes
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes
	Cisplatin	25mg/m^2	IV Infusion	In 500mL sodium chloride 0.9% over 60 minutes
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes

Concurrent CRT:

- **Cycles 1, 3 and 4 are SACT ONLY cycles**
- **Patients will undergo concurrent TWICE daily RT treatment schedule.** Refer to table below, outlining corresponding day of treatment and fraction(s) of radiotherapy.
- **Treatment should commence on a Monday afternoon to coincide with the first day of RT (cycle 2 ONLY)** 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.
- **SACT will be administered during the interval between the two RT fractions (6 to 8 hours).**
- **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.**

45Gy/30#/19days- TWICE daily RT

Treatment Day	Radiotherapy Fraction	Week day	Chemotherapy	Chemotherapy
1	1 and 2	MO	Etoposide	Cisplatin
2	3 and 4	TU	Etoposide	Cisplatin
3	5 and 6	WE	Etoposide	Cisplatin
4	7 and 8	TH		
5	9 and 10	FR		
6		SA		
7		SU		
8	11 and 12	MO		
9	13 and 14	TU		
10	15 and 16	WE		
11	17 and 18	TH		
12	19 and 20	FR		
13		SA		
14		SU		
15	21 and 22	MO		
16	23 and 24	TU		
17	25 and 26	WE		
18	27 and 28	TH		
19	29 and 30	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 **Days 1 to 3**
FBC	x	x	x	x	x	Every cycle **Day 1 ONLY**
U&E, LFTs & Magnesium	x	x	x	x	x	Every cycle **Day 1 ONLY unless clinically indicated (e.g. symptomatic of low sodium, potassium or magnesium)**
CrCl (Cockcroft and Gault)*	x	x	x	x	x	Every cycle **Day 1 ONLY unless clinically indicated e.g. AKI**
CT scan	x					At baseline then on completion of SACT and RT Or if clinically indicated
CT or MRI head	x					At baseline
ECG						If clinically indicated
Full observations *(BP, HR, RR and 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 calculating CrCl and 'Dose Modifications' section on recommendations on dosing.

Dose Modifications and Toxicity Management

Haematological Toxicity

Proceed on day 1 to 3 (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 cisplatin 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
Neurotoxicity	If patient develops Grade 2 neuropathy or ototoxicity, discuss with consultant. Patients with functional hearing loss should have cisplatin omitted, carboplatin AUC 3-5 can be substituted.

	Cumulative:-Dose related peripheral sensory neuropathy: Can occur after treatment with cisplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

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 Cisplatin 1mg/ml Intravenous Infusion, Accord – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated June 2021)
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

Date added into Q-Pulse	21st December 2022
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Version History

Date	Version	Author name and designation	Summary of main changes
	1.0	Hala Ghoz Lung SRG Pharmacist	New regimen protocol