SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Intravenous Topotecan Extensive-stage Small Cell Lung Cancer (ES-SCLC)

PROTOCOL REF: MPHAESSCLC
Version No.: 1.0

Approved for use in:

Relapsed extensive-stage small cell lung cancer (ES-SCLC) for whom:

- Re-treatment with the first-line regimen is not considered appropriate
- Combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated.

Please NOTE: For use ONLY while oral formulations unavailable

Funding:

Via NHSE. Blueteq form not required.

Dosage:

Drug	Dose	Route	Frequency	Duration
Topotecan	**1.5 mg/m^2**	IV infusion	Day 1 to 5 only Every 21 day	4-6 cycles but can be continued until progression or unacceptable toxicity* at the discretion of the clinical team.

***Recommend patients with complete or partial response at the first response assessment CT scan to continue treatment until disease progression or for two courses beyond best response.**

Administration:

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

- Signs of an infection such as fever; chills, cough, pain or burning when you pass urine.
- Easy bruising or bleeding.
- Signs of anaemia such as unusual tiredness, shortness of breath or weakness.
- Uncontrolled nausea, vomiting, constipation or diarrhoea.
- Severe abdominal or stomach cramping or pain.
- Shortness of breath or difficulty breathing.
- Redness, swelling, pain or sores where the needle was placed.
- Redness, swelling, pain or sores on your lips, tongue, mouth or throat.
- Skin rash or itching.

Emetogenic risk:

Moderate emetogenic.

Supportive treatments:

Metoclopramide 10mg oral up to three times a day for nausea and vomiting. Maximum for 5 consecutive days.

Ondansetron 8mg oral up to twice a day when required for nausea and vomiting (6 days supplied).

Filgrastim to be supplied as secondary prophylaxis - subcutaneous injection daily for 7 days starting on day 8, dose as follows:

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

Extravasation risk:

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

TOPOTECAN- IRRITANT

Dosing in renal and hepatic impairment:

Renal	GFR (ml/min)	Dose
	≥ 40	100%
	20-39	50%
	< 20 or on Haemodialysis	Not recommended, if unavoidable consider 25% of the original dose

Hepatic	Bilirubin ≤171 micomol/l: no dose adjustment required. Bilirubin >171 micomol/l: not recommended.

Interactions:

This list is not exhaustive, for more detailed interactions please refer to the BNF.

AGENT	SEVERITY	EFFECT	MANAGEMENT
Live Vaccines MMR Typhoid Varicella-zoster Yellow-fever Polio Rotavirus	Severe	Increase the risk of generalised infection	Contra-indicated Live vaccines should not be given during or within at least 6 months of treatment
Ciclosporin	Severe	Increased exposure to topotecan.	Discuss with clinical team prior to proceeding with SACT.
Clozapine	Severe	Increased myelosuppressive effect	Avoid if possible. If unavoidable increase frequency of FBC monitoring.
St John's Wort	Severe	Decreased topotecan exposure	Not to be taken together

Phenytoin	Moderate	Decreased topotecan exposure	May need to increase topotecan dose during concurrent therapy
Clarithromycin Itraconazole Ketoconazole Azithromycin Lopinavir Verapamil	Moderate	Increase exposure to topotecan.	Monitor for increase topotecan AEs (such as neutropenia and diarrhoea), and adjust the dose as necessary.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1 to 5	**Dexamethasone**	**8mg**	**PO**	30 minutes before chemotherapy
	Ondansetron	**8mg**	**PO**	30 minutes before chemotherapy
	Topotecan	**1.5 mg/m^2**	**IV**	Sodium Chloride 0.9% 50-100mL over 30 minutes

Main toxicities:

Topotecan	
Haematological	Dose-related myelosuppression (neutropenia, febrile neutropenia thrombocytopenia and anaemia, leucopenia) Severe myelosuppression leading to sepsis and fatalities. Topotecan-induced neutropenia can cause **neutropenic colitis which can be fatal.** In patients presenting with fever, neutropenia, and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.
GI disorders	Nausea, vomiting and diarrhoea (all of which may be severe), constipation, abdominal pain*, mucositis. *refer to haematological section above
Metabolism and nutrition disorders	Anorexia (which may be severe)
Hepatobiliary disorders	Hyperbilirubinaemia

Skin and subcutaneous tissue disorders	Alopecia Pruritis
General disorders and administration site conditions	Pyrexia, asthenia, fatigue Malaise
Pulmonary	Interstitial lung disease (ILD) is rare but can be fatal. Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic substances and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnoea and/or hypoxia).

Investigations and treatment plan:

	Pre	Cycle 1		Prior to cycle 2	Cycle 2		Cycle 3		Ongoing
		Day 1	Days 2-5		Day 1	Days 2-5	Day 1	Days 2-5	
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	x	x	Every cycle
Go-ahead/OTR	x				x		x		Every cycle Day 1 ONLY
FBC	x	x			x		x		Every cycle Day 1 ONLY unless clinically indicated
U&E & LFTs	x	x	x		x		x		
CrCl (Cockcroft and Gault)	x	x	x		x		x		
CT scan	x								After cycle 3 or if clinically indicated
ECG									If clinically indicated
Full Observations *(RR, BP, O2 saturation)*	x	x			x		x		Day 1 of every cycle and if clinically indicated
Weight recorded	x	x			x		x		Every cycle
Height	x								Repeat if clinically indicated

Monitor for:

- Pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnoea and/or hypoxia).
- **Neutropenic colitis** (fever, neutropenia, and a compatible pattern of abdominal pain)

Dose Modifications and Toxicity Management:

Table 1. Recommended topotecan dose reduction levels

Dose reduction level	Dose
First dose reduction	1.25 mg/m^2/day
Second dose reduction	1.0 mg/m^2/day

Topotecan should be discontinued if the dose had been reduced to 1.0 mg/m^2 and a further dose reduction was required to manage adverse effects.

Haematological toxicity:

Cycle 1 ONLY
Baseline haematological parameters prior to cycle 1 day 1 **should be as follows:**

ANC ≥ 1.5 x 10^9/L	Plt ≥ 100 x 10^9/L

NOTE: Severe bone marrow depression prior to starting first cycle, as evidenced by baseline neutrophils < 1.5 x 10^9/L and/or a platelet count of <100 x 10^9/L is a contraindication to treatment with topotecan.

Cycle 2 onwards

Proceed on day 1 to 5 if haematological parameters within the following parameters on day 1 (do not repeat FBC for days 2 to 5):

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 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.

Table 2: Dose modifications due to haematological toxicity

Adverse effect	Severity	Dose Modification
Severe neutropenia	ANC < 0.5 x 10^9/L for 7 days or more, or severe	Hold treatment until recovered to ≥ 1.0 x 10^9/L

	neutropenia associated with fever or infection, or patients who have had treatment delayed due to neutropenia.	After recovery, resume treatment at the next dose reduction level. **If neutropenia recurs despite first dose reduction then recommend the addition of GCSF prophylaxis with the next cycle.**
Severe thrombocytopenia	Plt < 25 x 10^9/L	Hold treatment until recovered to ≥ 100 x 10^9/L After recovery, resume treatment at the next dose reduction level.

Non- Haematological toxicity:

Adverse effect	Severity	Dose Modification
Any apart from nausea	Grade 3 or 4	Hold treatment until recovered to G1 or less. After recovery, resume treatment at the next dose reduction level.
Interstitial lung disease (ILD)	Any grade	Discontinue treatment.
Neutropenic colitis		Hold treatment and discuss with clinical team.

(Fever, neutropenia, and a compatible pattern of abdominal pain)		

References:

1. Eckardt, J. R., et al. (2007). Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *Journal of Clinical Oncology*, *25*(15), 2086-2092.
2. Horita, N., et al. (2015). Topotecan for relapsed small-cell lung cancer: systematic review and meta-analysis of 1347 patients. *Scientific reports*, 5(1), 1-8.
3. Topotecan 1 mg/ml concentrate for solution for infusion SmPC, Accord Healthcare Limited. Accessed via https://www.medicines.org.uk/emc/. Last updated 14th May 2021.
4. 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.
5. BNF available via: https://bnf.nice.org.uk/
6. NICE TA184: Topotecan for the treatment of relapsed small-cell lung cancer. Published date: November 2009.

Circulation/Dissemination

Date added into Q-Pulse	5th October 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Hala Ghoz **Lung SRG Pharmacist**	V1.0 New Regimen Protocol