PROTOCOL

Systemic Anti Cancer Therapy Protocol

Irinotecan and Temozolomide Sarcoma

PROTOCOL REF: MPHAIRITEM
(Version No. 1.1)

Approved for use in:

- Ewings sarcoma-2nd line onwards
- Rhabdomyosarcoma- 2nd line onwards

Dosage:

Drug	Dose	Route	Frequency
Irinotecan	**20 mg/m^2**	IV infusion	Day 1 to 5 and days 8 to 12 of a 21 day cycle
Temozolomide	**100 mg/m^2**	PO	Days 1 to 5 of a 21 cycle
Initially 6 cycles and review, may be continue until disease or unacceptable toxicity			

- Irinotecan dose may be reduced to 10mg/m^2
- Cycle must start on a **Monday** (unless an inpatient)

Emetogenic risk:

Moderate emetogenic.

Administration & Counselling Points:

<u>Temozolomide</u>

- Ensure patient knows exactly how and when to take them.
- Swallow whole with a glass of water on an empty stomach
- Take one hour before Irinotecan
- Do not add any missed doses onto the end of the cycle

Irinotecan

- Has the potential to cause severe diarrhoea
- Within 24 hours of irinotecan – likely caused by an acute cholinergic syndrome, and the patient should be advised to contact the triage team and attend for further atropine.
- Once a liquid stool occurs loperamide 4mg should be taken immediately, followed by 2mg every 2 hours for at least 12 hours, and for 12 hours following the last liquid stool. Patients should be instructed to drink large volumes of water or electrolytes. Do not continue high dose loperamide for longer than 48 hours Any concomitant fever or vomiting will require hospitalisaton for rehydration If diarrhoea persists after 48 hours then patients should be hospitalised for further management and treatment review. Do not use loperamide prophylactically even if delayed diarrhoea occurred in previous cycles.

Supportive treatments:

- Metoclopramide 10mg oral tablets three times a day if required
- Loperamide 4mg stat then 2mg every 2 hours, continuing for 12 hours after the last liquid stool. In no instance should loperamide be administered for more than 48 consecutive hours at these doses.

Extravasation risk:

Irinotecan- irritant

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

Dosing in renal and hepatic impairment:

Renal	Irinotecan	CrCL ≥ 10 ml/min: 100% CrCL < 10 ml/min 50% dose – increase if tolerated
	Temozolomide	No dose reduction needed

Hepatic	Irinotecan	Bilirubin 1.5-3 x ULN	50% Dose
		Bilirubin > 3 x ULN	Not recommended
	Temozolomide	No adjustment required	

Interactions:

Irinotecan

Concomitant use contraindicated

Saint John's Wort: Decrease in the active metabolite of irinotecan,

Live attenuated vaccines (e.g. yellow fever vaccine): Risk of generalised reaction to vaccines, possibly fatal. Concomitant use is contraindicated during treatment with irinotecan and for 6 months following discontinuation of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant use not recommended

Strong CYP3A4 and/or UGT1A1 inducing medicinal products (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin or apalutamide): Risk of reduced exposure to irinotecan. With phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal products.

CYP3A4 inhibitors (e.g. crizotinib, idelalisib): Risk of increase in irinotecan toxicity, due to a decrease in irinotecan metabolism.

Caution for use

Vitamin K antagonists: Increased risk of haemorrhage and thrombotic events in tumoural diseases. If vitamin K antagonists are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required.

Temozolomide

Administration of Temozolamide with food resulted in a decrease in exposure to the drug

Use of temozolomide in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Please refer to the SPC for more information.

Treatment schedule:

	Drug	Dose	Route	Diluent and rate
Days 1 / 2 / 3 / 4 / 5	**Temozolomide**	**100mg/m^2**	**PO**	60 minutes before irinotecan
	Dexamethasone	8mg	PO	30 minutes before irinotecan
	Ondansetron	16mg	PO	30 minutes before irinotecan
	Atropine	**600 micrograms**	**SC**	To be given if anticholinergic reaction occurs with irinotecan
	Irinotecan	**20mg/m^2**	**IV**	In 250mLglucose 5% over 30 minutes

	Drug	Dose	Route	Diluent and rate
Days 8 / 9 / 10 / 11/ 12	Dexamethasone	8mg	PO	30 minutes before irinotecan
	Ondansetron	16mg	PO	30 minutes before irinotecan
	Atropine	**600 micrograms**	**SC**	To be given if anticholinergic reaction occurs with irinotecan
	Irinotecan	**20 mg/m^2**	**IV**	In 250mLglucose 5% over 30 minutes

Main toxicities:

Irinotecan	
Blood disorders	Neutropenia, anaemia, thrombocytopenia
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, abdominal pain, constipation
Skin and tissue disorders	alopecia
Temozolomide	
Infections	Infections, herpes zoster, candidiasis oral
Blood system disorders	Neutropenia, thrombocytopenia, anaemia
Metabolism	Hyperglycaemia
Psychiatric disorders	Agitation, amnesia, insomnia
Skin disorders	Rash, alopecia
Gastrointestinal disorders	Diarrhea, constipation, nausea, vomiting

Please refer to the product SPC for more in depth information.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D8	Cycle 2	Cycle 2 D8	Ongoing
Informed Consent	X					
Clinical Assessment	X					As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities especially diarrhoea)	X	X	X	X	X	Every cycle
FBC	X	X		X		At the start of reery cycle. Not required for Day 8
U&E & LFTs & Magnesium	X	X		X		Every Cycle
CrCl (Cockcroft and Gault)	X	X		X		Every cycle
CT scan**	X					After cycle 2 and if clinically indicated
ECG	X					If clinically indicated
Main observations (Blood pressure measurement, respiratory rate)	X					Repeat if clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
Blood glucose	X					Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Repeat FBC **not** required on Day 8. Treatment on Day 8 is based upon bloods used for Day 1. However a toxicity review should be done on Day 8.

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.

If dose reduction is required, reduce irinotecan to 10mg/m^2

Non- Haematological toxicity:

Delayed diarrhea (24 hours post irinotecan)	For first episode of diarrhoea grade 1 or higher, delay treatment for 1 to 2 weeks until completely resolved and consider reducing dose of subsequent cycles to 10mg/m2 of irinoteca

References:

Summary of product of characteristics. *Irinotecan* www.medicines.org.uk/emc/product/6506/smpc [accessed on11/5/2023]

Summary of product of characteristics. *Temozolomide* www.medicines.org.uk/emc/product/5312/smpc [accessed on11/5/2023]

Casey DA, Wexler LH, Merchant MS, Chou AJ, Merola PR, Price AP, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience. Pediatric blood & cancer. 2009;53(6):1029- 34.

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

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
1.1	23/08/2023	**Rob Challoner (pharmacist)**	**Reviewed with Dr Ali. Patient counselling added. Renal / hepatic info simplified. Pre-meds added to treatment summary.**