Irinotecan and Temozolomide Therapy- 21 days[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of patients with relapsed/refractory Ewing's sarcoma	C41	00504a	N/A

*This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Irinotecan and temozolomide are administered on five consecutive days (days 1-5) of a 21 day cycle for 6 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1-5	Temozolomide	100mg/ m^2	PO [a,b,c]	N/A	Every 21 days for 6 cycles
1-5	Irinotecan	50mg/m^2	IV infusion	100mL NaCl 0.9% over 60 minutes	Every 21 days for 6 cycles
[a] Temozolomide hard capsules should be administered in the fasting state. The capsules must be swallowed whole with a glass of water and must not be opened or chewed. If vomiting occurs after the dose is administered, a second dose should not be administered that day.					
[b] Temozolomide should be administered at least one hour prior to irinotecan.					
[c] If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours.					

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate haematological, renal and liver status

CAUTION:

- In patients known to be homozygous for UGT1A1*28 consideration may be given to a reduced irinotecan starting dose

EXCLUSIONS:

- Hypersensitivity to irinotecan, temozolomide or to one of the excipients
- Chronic inflammatory bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Bilirubin > 3 x ULN

- Severe bone marrow failure
- Impaired renal function

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Virology screen - Hepatitis B (HBsAg, HBcoreAb)
  *(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- FBC, renal and liver profile prior to each cycle

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Table 1: Dose reduction levels for irinotecan and temozolomide

	Irinotecan	Temozolomide
Starting Dose	**50mg/m²**	**100mg/m²**
Level -1	40 mg/m² (80%)	80 mg/m² (80%)
Level -2	30 mg/m² (60%)	60 mg/m² (60%)
Level-3	Discontinue	Discontinue

Haematological:

- Preference should be given to the use of G-CSF support to maintain neutrophil counts rather than dose reduction.
- If significant toxicity continues despite G-CSF support, see Table 2 below for dose modifications.
  - Significant toxicity is defined by: Haematological recovery (ANC ≥1.0 x 10^9 /L, platelets ≥75 x 10^9 /L) delayed ≥14 days

Table 2: Dose modification for haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥ 1	and	≥ 75	100% Dose
< 1	and/or	< 75	If haematological recovery delayed for ≥14 days, reduce **temozolomide** dose by 1 dose level to Level-1 (see Table 1 above) for next cycle
Repeated episodes of febrile neutropenia Grade ≥ 3 after ≥ 2 cycles			Reduce **temozolomide** dose by 1 dose level to Level-1 (see Table 1) for next cycle
Further episodes of toxicity after reducing by 1 dose level			Reduce **temozolomide** dose further by 1 dose level (to Level-2). If toxicity recurs, discontinue study treatment

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Irinotecan[a]	**CrCl (mL/min)**	**Dose**	Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN	
	≥ 10	No need for dose adjustment is expected		
	< 10	Start with 50-66% of the original dose, increase if tolerated		
	Haemodialysis	Start with 50-66% of the original dose, increase if tolerated		
Temozolomide[b]	**CrCl (mL/min)**	**Dose**		**Dose**
	≥ 36	No dose adjustment is needed	Child-Pugh A/B	No dose adjustment is needed
	< 36	No need for dose adjustment is expected	Child-Pugh C	No need for dose adjustment is expected
	Haemodialysis	No need for dose adjustment is expected		

[a] Irinotecan (renal - Giraud et al 2023; hepatic as per SPC)
[b] Temozolamide (renal and hepatic - Giraud et al 2023)

Management of adverse events:

Table 4: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Diarrhoea	
• Grade ≥ 3 for ≥ 3 days despite symptomatic treatment	Reduce **irinotecan** dose by 1 dose level to Level-1 for next cycle If diarrhoea ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to < Grade 1 If Grade ≥ 3 diarrhoea persists > 2 weeks despite suitable symptomatic treatment, discontinue
• Grade ≥ 3 at reduced dose level (Dose level -1)	Reduce **irinotecan** dose further by 1 dose level to Level-2 for next cycle If diarrhoea ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to < Grade 1 If Grade ≥ 3 diarrhoea persists > 2 weeks despite suitable symptomatic treatment, discontinue
Other non-haematological toxicities:	
• Grade ≥ 3	Withhold both agents until toxicity resolves to ≤ Grade 2 If resolved to ≤ grade 2 by day 35 (i.e. after a delay of 1 week), resume treatment and reduce dose (of the agent responsible) by 1 dose level to Level-1 If neither agent is clearly responsible for toxicity, both to be reduced
• Grade ≥ 3 after 1 dose reduction (at Dose level -1) • Grade ≥ 3 after 2 dose reductions (at Dose level -2)	Reduce further by 1 dose level to Level-2 Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Irinotecan: Moderate **(Refer to local policy)**
Temozolomide: Moderate to High **(Refer to local policy)**

PREMEDICATIONS:

Prophylactic atropine sulphate – see adverse effects below.
Atropine should not be used in patients with glaucoma **(See Adverse Effects/Regimen specific complications below).**

OTHER SUPPORTIVE CARE:

- Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle
    - As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately
    - The currently recommended anti-diarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours)
    - This therapy should continue for 12 hours after the last liquid stool and should not be modified.
    - In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours
    - Noting that cefixime was used in the supporting trial, this agent may be considered in adults at a dose of 400 mg orally once daily from day-2 to day +7
- Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur
- PJP prophylaxis required with temozolomide **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.

Irinotecan:

- **Acute cholinergic syndrome**: If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation) atropine sulphate (0.25mg subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan. The dose of atropine sulphate may be repeated if required.
- **Diarrhoea:** Irinotecan induced diarrhoea can be life threatening and requires immediate management (See supportive care above also).
    - Diarrhoea (early onset) - see acute cholinergic syndrome above.
    - Diarrhoea (late onset):
        - Irinotecan induced diarrhoea can be life threatening and requires immediate management.
        - In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan
        - Patients with an increased risk of diarrhoea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women
        - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles
        - A prophylactic broad-spectrum antibiotic should be given, when diarrhoea is associated

with severe neutropenia (neutrophil count < 0.5 x 10^9/L)

- **Gilbert's Syndrome:** Increases the risk of irinotecan-induced toxicity. A reduced initial dose should be considered for these patients.
- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy.
- **Cardiac disorders:** Myocardial ischaemic events have been observed predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy.
- **Other:** Since this medicinal product contains sorbitol, it is unsuitable in hereditary fructose intolerance.

Temozolomide:

- **Opportunistic infections and reactivation of infections**: Opportunistic infections (such as Pneumocystis jirovecii pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with temozolomide.
- **Pneumocystis jirovecii pneumonia (PJP):** There may be a higher occurrence of PJP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PJP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using temozolomide, in particular in combination with dexamethasone or other steroids.
- **Hepatitis B Virus (HBV):** Hepatitis due to HBV reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.
- **Hepatotoxicity:** Hepatic injury, including fatal hepatic failure, has been reported in patients treated with temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide.

DRUG INTERACTIONS:

- CYP enzyme inducers may increase the clearance of irinotecan thus decreasing its efficacy.
- CYP enzyme inhibitors may decrease the clearance of irinotecan.
- No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other medicinal products.
- Since temozolomide does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	11/06/2024		Dr Mark Doherty

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.