FOLFOXIRI Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of metastatic colorectal cancer	C18	00555a	Hospital

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.

Treatment is administered every 14 days 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	Irinotecan	165mg/m^2	IV infusion	250ml 0.9% NaCl over 90mins	Repeat every 14 days
1	Oxaliplatin	85 mg/m^2	IV infusion	500ml 5% glucose over 2 hours[a] (after irinotecan). Administer concurrently with folinic acid in separate bags via y-line connection	Repeat every 14 days
1	Folinic Acid (Calcium leucovorin)	200mg/m^2	IV infusion	250ml 5% glucose over 2 hours, administer concurrent with oxaliplatin	Repeat every 14 days
1	5-Fluorouracil[b]	3200mg/m^2	Continuous IV infusion	Over 48 hours in 0.9% NaCl (equivalent to 1600mg/m^2/day)	Repeat every 14 days
Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline. For oxaliplatin doses ≤ 104mg use 250ml glucose 5%. [a]Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction. Oxaliplatin administration must always precede the administration of 5-Fluorouracil.					
Folinic Acid *(Calcium Leucovorin)* must be administered prior to 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-Fluorouracil binding to the target enzyme thymidylate synthetase					
[b]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency					

ELIGIBILITY:

- Indications as above
- ECOG ≤2 (adults under 70 years)
- ECOG <1 (adults 71-75)
- Adequate haematological, renal and liver status

CAUTION:

Use with caution in patients with

- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Symptomatic peripheral neuropathy

EXCLUSIONS:

- Hypersensitivity to irinotecan, oxaliplatin, 5-Fluorouracil or any of the excipients
- Baseline neutrophils < 2 x 10^9/L and/or platelet count < 100 x 10^9/L
- Severe renal impairment (creatinine clearance < 30ml/min)
- Bilirubin > 3 x ULN
- Chronic bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Severe bone marrow failure
- CNS metastases
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Blood, liver and renal profile
- ECG (if patient has compromised cardiac function)
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- Blood, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every cycle prior to proceeding with treatment

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:

- Consider a reduced starting dose in patients with identified partial DPD deficiency
    - Initial dose reduction may impact the efficacy of treatment
    - In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Any dose modification should be discussed with a Consultant

Haematological

- Treatment is not administered unless ANC ≥1.5 x 10^9L and platelets ≥75 x 10^9/L
- If levels are below this at Day 1 treatment may be delayed for 1-2 weeks
- If no recovery in 2 weeks consideration should be given to discontinuing the treatment

Table 1: Dose modification of FOLFOXIRI based on Day 1 Absolute Neutrophil Count (ANC)

ANC < 1.5 x 10^9/L	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence	Reduce dose to 150mg/m^2	Maintain full dose	Reduce to 75% of the original dose
2nd occurrence	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	Reduce to 50% of the original dose
3rd occurrence	DISCONTINUE TREATMENT		

Table 2: Dose modification of FOLFOXIRI based on Day 1 Platelet Count

Platelets < 75 x10^9/L	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence	Maintain full dose	Reduce to 60mg/m^2	Reduce to 75% of the original dose
2nd occurrence	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	
3rd occurrence	DISCONTINUE TREATMENT		

Table 3: Dose modification of FOLFOXIRI based on low nadir blood counts or in case of infection

Platelets < 50 x10^9/L	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence	Maintain full dose	Reduce to 60mg/m^2	Reduce to 75% of the original dose
2nd occurrence	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	Reduce to 50% of the original dose
3rd occurrence	DISCONTINUE TREATMENT		

Renal and Hepatic Impairment:

Table 4: Recommended dose modifications for patients with renal or hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td rowspan="3">Oxaliplatin</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="4" rowspan="3">Little information available.
Probably no dose reduction necessary.
Clinical decision.</td></tr>
<tr><td>≥30</td><td>Treat at normal dose and monitor renal function</td></tr>
<tr><td><30</td><td>Contraindicated</td></tr>
<tr><td>Irinotecan</td><td colspan="2">No dose reduction needed, however use with caution as no information in this setting.</td><td colspan="4">Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN</td></tr>
<tr><td rowspan="4">5-Fluorouracil</td><td colspan="2" rowspan="4">Consider dose reduction in severe renal impairment only</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>Contraindicated</td></tr>
<tr><td colspan="4">Clinical decision.
Moderate hepatic impairment; reduce initial dose by 1/3.
Severe hepatic impairment, reduce initial dose by 1/2.
Increase dose if no toxicity.</td></tr>
</table>

Management of adverse events:

Table 5: Recommended dose modification schedule based on non-haematological, non-neurological toxicities

Prior to a Cycle (DAY 1)	Irinotecan	Dose Level for Subsequent Cycles	
		Oxaliplatin	5-Fluorouracil
Diarrhoea			
• **1st occurrence** ○ Grade 3 or 4 ○ With fever and/or Grade 3 or 4 neutropenia	Reduce dose to 150mg/m^2		Reduce to 75% of original dose
• **2nd occurrence**		Reduce dose to 60mg/m^2	Reduce to 50% of the original dose
• **3rd occurrence**	DISCONTINUE TREATMENT		
Mucositis or hand-foot syndrome Grade 3 or 4			Reduce to 75% of original dose
Other toxicity • ≥ Grade 2 (except alopecia and anaemia)	Consider dose reduction		
• Transient grade 3 paresthesias/dysesthesias or transient grade 2 symptoms lasting > 7 days		Decrease oxaliplatin by 25%	
• Grade 4 or persistent grade 3		Discontinue oxaliplatin	
Laryngo-pharyngeal dysaesthesia		Increase infusion time from 2 to 6 hours	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: This regimen poses an overall high risk of emesis

Irinotecan: Moderate **(Refer to local policy)**
Oxaliplatin: Moderate **(Refer to local policy)**
5-Fluorouracil: Low **(Refer to local policy)**

PREMEDICATIONS:

Prophylactic atropine sulphate 250micrograms subcutaneously – 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

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.

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.

Oxaliplatin

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-Fluorouracil.
- **Extravasation:** Oxaliplatin causes irritation if extravasated **(Refer to local policy).**
- **Venous occlusive disease:** A rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with 5-Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
- **Haemolytic Ureamic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

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 (250 micrograms 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**.**
- **Diarrhoea -** Irinotecan induced diarrhoea can be life threatening and requires immediate management.
    - 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.
  - The SmPC (11) provides guidelines on when hospitalisation for the management of diarrhoea is recommended.
- **Extravasation:** Irinotecan causes pain and tissue necrosis if extravasated**. (Refer to local extravasation guidelines).**
- **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.

5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE), has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil (see table 5 for dose modifications).

DRUG INTERACTIONS:

- Risk of drug interactions causing decreased concentrations of irinotecan with CYP3A inducers.
- Risk of drug interactions causing increased concentrations of irinotecan with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimes.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil-metabolising enzyme DPD
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	18/03/2019		Prof Maccon Keane
2	12/02/2020	Standardisation of treatment table. Updated exclusions and drug interactions. Updated recommended dose modifications for oxaliplatin in renal impairment.	Prof Maccon Keane
3	3/9/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane
4	10/03/2021	Reviewed. Amended exclusions and emetogenic potential.	Prof Maccon Keane
5	21/07/2021	Clarification of administration details	Prof Maccon Keane
6	05/09/2022	Updated emetogenic potential.	Prof Maccon Keane
6a	23/11/2023	Formatting changes and grammatical corrections.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.