FOLFIRINOX Therapy - (Rectal Carcinoma)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement Status*
Neoadjuvant chemotherapy for locally advanced rectal cancer	C18	00691a	N/A

*This applies to 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.

Treatment is administered every 14 days for 6 cycles unless progression or unacceptable toxicity develops. This is followed by 5 weeks of chemoradiotherapy.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Oxaliplatin[a]	85 mg/m^2	IV infusion	500mL 5% glucose over 2 hours immediately followed by:	Repeat every 14 days for 6 cycles
1	Folinic Acid[b] (Calcium leucovorin)	[c]400mg/m^2	IV infusion	250mL 0.9% NaCl over 2 hours with the addition after 30 minutes of irinotecan as below	Repeat every 14 days for 6 cycles
1	Irinotecan	180mg/m^2	IV infusion	250mL 0.9% NaCl over 90 minutes given through a Y connector placed immediately before the injection site Immediately followed by:	Repeat every 14 days for 6 cycles
1	5-Fluorouracil[d]	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	Repeat every 14 days for 6 cycles

[a]Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.
For oxaliplatin doses ≤ 104mg use 250mL glucose 5%.
Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction.
Oxaliplatin administration must always precede the administration of 5-Fluorouracil.

[b] Folinic Acid *(Calcium Leucovorin)* must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase.

[c] A dose of 200mg/m^2 of folinic acid may be considered.

[d] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Followed by:

Day	Drug	Dose	Route	Cycle
1-5	Capecitabine	800 mg/m^2 Twice daily[a,b,c,d]	PO	Every 7 days for 5 cycles with radiotherapy
[a]The dose to be administered should consider the available tablet strengths. Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine- Available on the NCCP website. Tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. Tablets should not be crushed or cut. [b] (total daily dose = 1600mg/m^2) [c] Consideration may also be given to the use of Capecitabine 825mg/m^2 twice daily as per NCCP Regimen 00586a at the discretion of the prescribing Consultant.				
[d] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.				

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate haematological, renal and liver function

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
- In patients known to be homozygous for UGT1A1*28 consideration may be given to a reduced irinotecan starting dose
- Chronic bowel disease and/or bowel obstruction
- CNS metastases

EXCLUSIONS:

- Hypersensitivity to irinotecan, oxaliplatin, 5-fluorouracil, capecitabine or any of the excipients
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Baseline neutrophils < 1.5 x 10^9/L and/or platelet count < 100 x 10^9/L
- Bilirubin > 3 x ULN
- Pregnancy and lactation
- Known complete DPD deficiency
- Recent or concomitant treatment with brivudine

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
    - In patients with moderate or severe renal impairment, blood uracil levels used for DPD phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment

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:

- Any dose modification should be discussed with a Consultant
- Consider a reduced starting dose for 5-Fluorouracil and capecitabine 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
- Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction)
    - Once the dose has been reduced, it should not be increased at a later time
    - For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption
    - Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs
    - Doses of capecitabine omitted for toxicity are not replaced

Haematological

- Treatment is not administered unless ANC ≥1.5 x 10^9/L and platelets ≥100 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 FOLFIRINOX based on Day 1 Absolute Neutrophil Count (ANC)

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of ANC < 1.5 x 10^9/L	Reduce dose to 150mg/m^2	Maintain full dose	Maintain full dose
*2nd occurrence of ANC < 1.5 x 10^9/L	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	-
3rd occurrence ANC < 1.5 x 10^9/L	Discontinue	-	-

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

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of platelets < 100 x10^9/L	Maintain full dose	Reduce to 60mg/m^2	Reduce continuous infusion dose by 25%
2nd occurrence of platelets < 100 x10^9/L	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	-
3rd occurrence of platelets < 100 x10^9/L	-	Discontinue	-

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

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of: • Febrile neutropenia • ANC < 0.5 x 10^9/L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	Reduce dose to 150mg/m^2	Maintain full dose	Maintain full dose
2nd occurrence of: • Febrile neutropenia • ANC < 0.5 x 10^9/L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	Reduce continuous infusion to 2000mg/m^2
3rd occurrence • Febrile neutropenia • ANC < 0.5 x 10^9/L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	Discontinue treatment		
1st occurrence of Platelets < 50x 10^9/L	Maintain full dose	Reduce to 60mg/m^2	Maintain full dose
2nd occurrence of Platelets < 50x 10^9/L	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	Reduce infusion dose by 25%
3rd occurrence of Platelets < 50x 10^9/L	Discontinue treatment		

*For any febrile neutropenia or a 2nd episode of ANC < 1x10^9/L. G-CSF prophylaxis should be considered for subsequent cycles.

Renal and Hepatic Impairment:

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

Drug	Renal impairment		Hepatic impairment			
Oxaliplatin	**CrCl (mL/min)**	**Dose**	No dose adjustment is needed			
	≥30	No dose adjustment is needed				
	<30	Consider 50% of original dose				
	Haemodialysis	Consider 50% of original dose, haemodialysis within 90 mins after administration				
Irinotecan	**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 original dose, increase if tolerated				
	Haemodialysis	Start with 50-66% of original dose, increase if tolerated				
5-Fluorouracil	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		**Bilirubin (micromol/L)**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Contraindicated
			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.			
Capecitabine	**CrCl (mL/min)**	**Dose**	No dose adjustment is needed.			
	51-80	100% dose				
	30-50	75% dose				
	< 30	Not recommended				
	Haemodialysis	Not recommended				

Management of adverse events:

Table 5: Dose Modifications for Oxaliplatin* NEUROLOGICAL Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1-7 days	> 7 days	
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Maintain dose level	Maintain dose level	↓ 1 dose level
3	65mg/m^2	65mg/m^2	Discontinue therapy
4	Discontinue therapy		
Laryngo-pharyngeal dysaesthesia	Maintain dose level. Increase infusion time from 2 to 6 hrs		
***If oxaliplatin is discontinued due to neurotoxicity, irinotecan and 5-Fluorouracil are continued**			

Table 6: Dose modification schedule based on non-haematological, non-neurological toxicities

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
Grade 3-4 diarrhoea OR Diarrhoea, fever and/or ANC < 1 x 10^9 /L			
• 1st occurrence	Reduce dose to 150mg/m^2	Maintain full dose	Maintain full dose
• 2nd occurrence	Maintain dose at 150mg/m^2	Reduce dose to 60mg/m^2	Reduce continuous infusion by 25%
• 3rd occurrence	Discontinue	-	-
Persistent diarrhoea (>48h) despite high doses of loperamide	No reduction in irinotecan or oxaliplatin or 5-Fluorouracil dose after recovery **unless** grade 3-4 diarrhoea, or diarrhoea + fever and/or grade 3-4 neutropenia		
Mucositis or "hand foot" syndrome Grade 3 or 4			Reduce continuous infusion by 25% for subsequent cycles

Elevation of Bilirubin:

Elevation of bilirubin should be investigated to determine the cause and the dose of irinotecan should be adjusted if medically indicated.

Table 7: Dose modification schedule based on elevated bilirubin

Bilirubin	Dose reduction at next cycle
27-50 micromol/L	Reduce the irinotecan dose to 50%
>50 micromol/L	Stop irinotecan

Table 8: Dose modification of capecitabine due to toxicity

Toxicity NCI Grade	Discontinuation of capecitabine	Modification of dose
Grade 1	No	No
Grade 2 1st episode	Hold treatment until resolves to grade 0-1	Reduce dose to 600mg/m^2 twice daily
Grade 2 2ndepisode	Hold treatment until resolves to grade 0-1	Reduce dose to 400mg/m^2 twice daily
Grade 2 3rd episode	Hold treatment until resolves to grade 0-1	
Grade 3	As for grade 2	
Grade 4	Definitive discontinuation or hold until resolves to grade 0-1	
Angina, infarction	Definitive discontinuation	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting - available on the NCCP website

This regimen poses an overall high risk of emesis

5-Fluorouracil: Low (**Refer to local policy).**
Irinotecan: Moderate (**Refer to local policy).**
Oxaliplatin: Moderate (**Refer to local policy).**
Capecitabine: Minimal to low **(Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - available on the NCCP website

PREMEDICATIONS:

Prophylactic atropine sulphate 250micrograms subcutaneously – see adverse effects below.
Atropine should not be used in patients with glaucoma **(See Regimen specific complications below).**

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment **(Refer to local policy).**
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:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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.

- **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**.**

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	30/03/2022		Prof Maccon Keane
2	05/09/2022	Updated emetogenic potential	Prof Maccon Keane
3	09/04/2024	Reviewed. Updated eligibility section, renal and hepatic dose modifications and drug interactions section.	Prof Maccon Keane
4	24/02/2025	Updated testing section. Updated wording in table 2 and Table 6. Updated regimen in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.