FOLFIRI- Irinotecan and Modified de Gramont Fluorouracil

Indication

Palliative treatment of metastatic colorectal cancer

Neoadjuvant treatment of metastatic or inoperable colorectal cancer

Regimen details

Day	Drug	Dose	Route
1	Irinotecan	180mg/m^2	IV infusion
1	Folinic Acid	350mg	IV infusion
1	5-Fluorouracil	400mg/m^2	IV bolus
1-2 (46 hours)	5 Fluorouracil	2400mg/m^2	IV infusor pump over 46 hours

Pre-medication

Nb Atropine 250mcg sc *must* be prescribed before treatment commences.
This is to be administered in the event of a cholinergic reaction unless the patient has experienced such a reaction in a previous cycle (give 30 minutes prior to irinotecan).

Cycle frequency

14 days

Number of cycles

Palliative until disease progression or unacceptable toxicity
Neo-adjuvant 6 cycles

Administration

Folinic acid is administered in 250ml glucose 5% over 2 hours.
Irinotecan is administered in 250mL sodium chloride 0.9% over 30 minutes.
Fluorouracil is administered as an IV bolus injection over 5 minutes.
Administer atropine 250mcg s/c if patient experiences cholinergic reaction with first cycle
Warning: administering irinotecan and folinic acid concurrently in the same line may result in precipitation

Emetogenicity

Moderate emetogenic potential

Additional supportive medication

Mouthwash as per local policy
All patients must have access to loperamide with the advice to take 4mg at the onset of diarrhoea and to continue taking 2mg every 2 hours for at least 12 hours to a maximum of 48 hours (up to a maximum of 24mg/24 hours).

Extravasation

Irinotecan is an irritant (Group 3).
Fluorouracil is an inflammatant (Group 2)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs (including AST)	14 days
Calcium	14 days
Magnesium	14 days
CEA	14 days
DPYD mutation testing	none
Hepatitis B serology (HBsAG, HBcAb)	none
HbA1c	3 months
Random glucose	14 days
ECG	28 days
Calculated Creatinine Clearance	14 days

Investigations –pre subsequent cycles

FBC, U&Es, LFT (including AST), calculated creatinine clearance, calcium, magnesium, random glucose, CEA

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L (discuss with consultant ≥ 1.0- <1.5)
Platelets	≥ 75 x 10^9/L
Bilirubin	< 1.5 x ULN
AST/ALT	< 1.5 x ULN
Creatinine Clearance (CrCl)	≥ 30mL/min (see dose modifications below)

For treatment with neoadjuvant intent consultants may be happy to proceed with Neutrophils ≥1.0 x 10^9/L and should document this.

Dose modifications

- **DPYD variants**

All patients due to receive fluoro-pyrimidine based therapy should have a DPD test prior to starting treatment. Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle).

Any patient who has not had a DPD test should be discussed with the consultant prior to going ahead. Patients with variants should be considered for a dose modification following national advice for recommended dose adjustments.

https://www.uksactboard.org/_files/ugd/638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf

Where a patient has had significant toxicities but the DPD test has shown none of the variants to be present, a further test can be conducted to test the presence of rarer variants.

- **Haematological toxicity**

Defer treatment for 1 week if neutrophil count <1.0 x 10^9/L and/or platelets <75 x 10^9/L.
If there is >1 week delay due to haematological toxicity reduce irinotecan to150mg/m2 and fluorouracil doses to 80%.

If febrile neutropenia (neutrophils < 0.5 x 10^9 /L and fever requiring IV antibiotics) – reduce all subsequent doses of fluorouracil to 50% and irinotecan dose to 120mg/m^2.

Continue at reduced dose for subsequent cycles unless other toxicity occurs

If further delays for bone marrow suppression occur despite a 20% dose reduction consider further 20% dose reduction

- **Renal impairment**

Creatinine Clearance (ml/min)	Fluorouracil dose	Irinotecan dose
>30	100%	100%
<30	80%	omit

Irinotecan is not recommended for use in patients with impaired renal function

- **Hepatic impairment**

Bilirubin (xULN)		AST/ALT (x ULN)	Fluorouracil dose	Irinotecan dose
<1.5	and	< 1.5	100%	100%
1.5-3	or	1.5-3	Consider dose reduction*	50%
3-5	or	3-5	Consider dose reduction*	Contraindicated
>5	or	>5	Contraindicated	Contraindicated

*consultant decision
Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment.

- **Other toxicities**

Diarrhoea

Immediate (within 24 hours)	Incidence low due to use of atropine pre-med	Further dose of atropine 250 mcg stat
Delayed (>24 hours after irinotecan up to any time before next cycle)	Initial treatment	Treat early with high dose loperamide (up to a max of 24mg/24 hr)
	Lasts >24 hours	Add ciprofloxacin 500mg bd
	Lasts >48 hours	If >48 hours or symptoms of dehydration admit for rehydration and supportive management
	Grade 3-4	Manage as above, then delay further treatment until recovery then resume as in table below
	Unresolved before next cycle	Delay 1 week

If diarrhoea from the previous cycle (even if not severe) has not resolved (without loperamide for at least 24 hours), by the time the next cycle is due, delay 1 week.

If resolved to grade 2 or less within 2 weeks continue treatment with the following dose reductions:

Toxicity Definition	Irinotecan dose	Fluorouracil dose
Grade 3	150mg/m^2	Omit bolus
Grade 4	120mg/m^2	Omit bolus and reduce infusion to 75% dose

If diarrhoea persists after 2 weeks at grade 3 or 4 discontinue treatment

Patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared as a rapid deterioration can occur.

Stomatitis

Treatment should be delayed until resolved to ≤ grade 1 and then doses reduced as follows:

Toxicity definition	Fluorouracil dose
Grade 2	80%
Grade 3	50%
Grade 4	Discontinue or 50% (consultant decision)

Palmar plantar erythema:
Treat symptomatically and treatment should be delayed until ≤ grade 1. Reduce doses as follows:

Toxicity definition	Fluorouracil dose
Grade 2	80%
Grade 3-4	50%

Other dose modifications should be made as per the following table

Toxicity grade	1st occurrence	2nd occurrence	3rd occurrence	4th occurrence
0-1	100%	100%	100%	100%
2	Delay then 100%	Delay then 75%	Delay then 50%	Discontinue
3	Delay then 75%	Delay then 50%	Discontinue	
4	Delay then 50%	Discontinue		

Any delays should be until toxicity has resolved to grade 0-1

Hand foot syndrome ≥grade 2: 20% dose reduction of 5FU, irinotecan full dose

Adverse effects - for full details consult product literature/ reference texts

• Serious side effects

Myelosuppression
Infertility
Ocular toxicity
Severe diarrhoea
Coronary artery spasm*

*Coronary artery spasm is a recognised complication of fluorouracil treatment, although the evidence base regarding aetiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of fluorouracil and is usually reversible on discontinuing the infusion. Should a patient receiving fluorouracil present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the fluorouracil should be permanently discontinued.

• Frequently occurring side effects

Myelosuppression
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema Alopecia

• Other side effects

Transient cerebellar syndrome
Confusion

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.
Irinotecan: Irinotecan is a major substrate of **cytochrome P450 CYP2B6 and CYP3A4** and as such levels of irinotecan may be reduced by medicines that induce levels of these enzymes. Conversely, levels of irinotecan may be increased by medicines that inhibit these enzymes.
Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
Fluorouracil: Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of fluorouracil.
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.

Fertility/Contraception

Patients should agree to use an acceptable method of birth control to avoid pregnancy for the duration of treatment and for 6 months afterwards. Breast feeding should be discontinued during treatment. There is no data on fertility effect of irinotecan.

References

- Tournigand C, André T, Achile E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004 22(2): 229-37.
- Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 9 May 2025 via www.nice.org.uk
- Summary of Product Characteristics Irinotecan accessed 9 May 2025 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil accessed 9 May 2025 via www.medicines.org.uk

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON, DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: May 2025
Review: May 2027
VERSION: 18