FOLFIRI - Irinotecan and Modified de Gramont Fluorouracil (colorectal)

Indication

First or second line treatment of advanced metastatic colorectal cancer.

WH0 performance status 0-1.

(NICE CG131)

ICD-10 codes

Codes prefixed with C18-20.

Regimen details

Day	Drug	Dose	Route
1	Calcium folinate	350mg	IV infusion
1	Irinotecan	180mg/m^2	IV infusion
1	Fluorouracil	400mg/m^2	IV bolus
1-2 (46 hours)	Fluorouracil	2400mg/m^2	IV infusion over 46 hours

Cycle frequency

14 days

Number of cycles

6 cycles then review. Maximum 12 cycles.

Administration

Calcium folinate is administered in 250-500mL sodium chloride 0.9% or glucose 5% over 2 hours. This is either administered first or concurrently with the irinotecan via a Y-site connector.

Irinotecan is administered in 250mL sodium chloride 0.9% over 30 – 90 minutes. The first dose must be administered over 90 minutes. If this is well tolerated subsequent doses may be administered over 30 minutes.

Fluorouracil is administered as an IV bolus injection over 5 minutes.
Fluorouracil infusion is administered either via a central venous catheter and ambulatory infusion device over 46 hours or as a continuous peripheral IV infusion over 46 hours in 2 x 1000mL sodium chloride 0.9%.

Pre-medication

Atropine 250 microgram SC 30 minutes prior to irinotecan administration to control anticholinergic syndrome. An additional dose may be given if this develops.

Emetogenicity

This regimen has a moderate emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Loperamide if required.
Ciprofloxacin 250 mg BD for 5 days if diarrhoea persists for more than 24 hours.

Prophylactic ciprofloxacin should also be commenced in patients with neutrophils <0.5 x 10^9/L, even in the absence of diarrhoea. Patients who develop severe neutropenia are especially at risk of infection if they are also suffering from diarrhoea.

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	14 days
CEA	14 days

Investigations - pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days

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	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Bilirubin	< 1.5 x ULN
AST/ALT	< 1.5 x ULN
Creatinine Clearance (CrCl)	≥ 30mL/min

Dose modifications

- **Haematological toxicity**

Defer treatment for 1 weeks if neutrophil count <1.0 x 10^9/L and/or platelets <100 x 10^9/L. If there is > 1 week delay due to haematological toxicity reduce irinotecan to150mg/m^2 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.

- **Renal impairment**

CrCl (mL/min)	**Irinotecan dose**	**Fluorouracil dose**
≥ 30	100%	100%
10-29	50%	100%
<10	50%	Consider dose reduction (consultant decision)

- **Hepatic impairment**

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

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.

Diarrhoea may be life-threatening and requires prompt, aggressive treatment:

• Early diarrhoea or abdominal cramps occurring within the first 24 hours should be treated with atropine 0.3 - 1.2 mg IV or SC. DO NOT ADMINISTER LOPERAMIDE DURING THIS 24 HOUR PERIOD.

• Late diarrhoea (diarrhoea occurring >24 hours after treatment) must be treated with loperamide; 4mg at the first loose stool and then 2mg every 2 hours until diarrhoea-free for 12 hours after last loose stool (4 mg every 4 hours may be taken over night). Note: this dose is higher than recommended by the manufacturer. If diarrhoea persists for >24 hours ciprofloxacin 500 mg BD should be commenced. Loperamide must not be administered for more than 48 consecutive hours at these doses without appropriate medical supervision due to the risk of paralytic ileus.

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%

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.

Additional comments

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). Contraindicated in patients with known DPD deficiency.

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

References

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