Irinotecan and Capecitabine (CAPIRI)

Indication

Metastatic colorectal cancer

Regimen details

Day	Drug	Dose	Route
1	Irinotecan	250mg/m^2	IV infusion
1-14	Capecitabine	1000mg/m^2 BD	PO

In patients aged 65+ years, reduction in starting dose of capecitabine to 800mg/m^2 is recommended

Cycle frequency

21 days

Number of cycles

Until disease progression or unacceptable toxicity

Administration

Patient must be able to comply with oral chemotherapy regimen.
Patients should take capecitabine within 30 minutes after a meal
Any unused tablets to be returned at the next appointment

Cycle must finish 14 days after starting irrespective of how many delays or tablets not taken

Irinotecan is given over 30-90 minutes

Pre-medication

Atropine 250mcg must be prescribed before treatment commences. This is only to be administered in the event of a cholinergic reaction unless the patient has experienced such a reaction in a previous cycle

Emetogenicity

This regime has a moderate emetogenic potential

Additional supportive medication

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 (up to a maximum of 24mg/24 hours).

Extravasation

Irinotecan is an Irritant (Group 3)

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)	≥ 50mL/min (see dose modifications below)

If only Hb is low (below 95g/dl) please contact doctor to arrange for blood transfusion but continue with chemotherapy.

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

Patients that are UGT1A1 poor metabolisers, such as patients with Gilbert's syndrome (eg

homozygous for UGT1A1*28 or *6 variants) are at increased risk for severe neutropenia and diarrhoea following irinotecan treatment. This risk increases with irinotecan dose level. A reduced starting dose should be considered.

- **Renal impairment**

Creatinine Clearance (ml/min)	Capecitabine dose	Irinotecan dose
>50	100%	100%
30-50	75%	Discuss with consultant
<30	Contraindicated	Omit

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

- **Hepatic impairment**

Irinotecan and metabolites are cleared by biliary excretion. Data is not available in patients with hepatic impairment treated with irinotecan in combination.
Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment.
Weekly monitoring of complete blood counts should be considered in patients with bilirubin from 1.5 to 3 times ULN due to decrease in the clearance of irinotecan and increased risk of hepatotoxicity in this population.

Bilirubin	ALT	Capecitabine dose	Irinotecan dose
<1.5 x ULN **and**	≤ 2.5 x ULN	100%	100%
<1.5 x ULN **and**	2.5-5 x ULN	Withhold and discuss with consultant	100%
1.5-3 x ULN **and**	≤2.5 x ULN	100%	50%
1.5-3 x ULN **and**	2.5-5 x ULN	Withhold and discuss with consultant	50%
1.5-3 x ULN **or**	>5 x ULN	Withhold and discuss with consultant	50%
>3 x ULN **and**	any	Withhold and discuss with consultant	Omit

- **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 consider reducing irinotecan and/or capecitabine dose to 80%.

If febrile neutropenia (neutrophils < 0.5 x 10^9 /L and fever requiring IV antibiotics) – reduce subsequent doses of irinotecan and/or capecitabine to 80%.

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

- **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 anytime 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 at irinotecan 80% dose capecitabine 80% dose
	Unresolved before next cycle	Delay 1 week

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

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 capecitabine, irinotecan full dose

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Ocular toxicity
Severe diarrhoea
Anaphylaxis
Interstitial lung disease
Coronary artery spasm*

*Coronary artery spasm is a recognised complication of capecitabine treatment, although the evidence base regarding aetiology, management and prognosis is not particularly strong.
Should a patient receiving capecitabine 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 capecitabine should be permanently discontinued.

• Frequently occurring side effects

Myelosuppression
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema
Alopecia
Veno-occlusive disease
Infusion reactions
Acute cholinergic syndrome

• Other side effects

Headache
Dizziness
Dysgeusia
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.

Capecitabine:

Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of capecitabine.
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Phenytoin and fosphenytoin: Toxicity has occurred during concomitant therapy- monitor levels regularly
Sorivudine and its analogues: Co-administration can cause increased toxicity which may be fatal.
Allopurinol: A decrease in capecitabine activity has been shown when taken in combination with allopurinol. Avoid if possible
Antacids: the use of antacids with capecitabine can decrease absorption-avoid.

Additional comments

Patients with chronic inflammatory bowel disease and/or bowel obstruction should not be treated with irinotecan until resolution of the bowel obstruction.

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. Breastfeeding should be discontinued during treatment. There is no data on fertility effect of irinotecan,

References

- Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 9 May 2025 via www.nice.org.uk
- Summary of Product Characteristics Irinotecan accessed 23 June 2025 via www.medicines.org.uk
- Summary of Product Characteristics Capecitabine accessed 23 June 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: June 2025
Review: June 2027
VERSION: 10