Irinotecan and Capecitabine (CAPIRI)

Indication
Metastatic colorectal cancer

Regimen details

Irinotecan 250mg/m^2 in 250ml 0.9% sodium chloride over 30 minutes
Capecitabine 1000mg/m^2 twice daily for 14 days

Cycle frequency
Every 21 days

Number of cycles
Until disease progression

Administration
Patients should take capecitabine within 30 minutes after a meal

Administer atropine 0.25mg s/c if patient experiences cholinergic reaction with first cycle

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).

Patient must be able to comply with oral chemotherapy regimen

Patients should be informed of the need to interrupt treatment immediately if they develop moderate or severe side effects, particularly diarrhoea (not controlled by loperamide), palmar plantar erythrodyaesthesia, chest pain or infection.

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

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
Moderate

Additional supportive medication
Loperamide

Extravasation
Irritant

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days

LFT (including AST)	14 days
Bone profile	14 days
CEA	14 days
Coagulation profile	14 days
CT scan	As appropriate
DPYD Screen	

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). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST)
Calcium and CEA every 2nd cycle

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophil count	≥ 1.5 x 10^9/L (if neutrophils 1.2 – 1.5 x10^9/l contact consultant)
Platelet count	≥ 100 x 10^9/L
Hb	≥ 95 g/l
Creatinine clearance	≥ 50 mL/min
Bilirubin	≤ 1.5 x ULN
Alk Phos	<5x ULN

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

Dose modifications

Age ≥ 70 years – reduce Capecitabine to 750 mg/m^2 (max 1500 mg bd)

Renal Impairment

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

Hepatic Impairment
Irinotecan and metabolites are cleared by biliary excretion
Delayed clearance in cholestasis

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

Grade I/II ANC — No dose reduction
Grade III/IV — Delay until recovered then proceed with 20% Irinotecan and capecitabine reduction
If delay >1 week — reduce capecitabine and irinotecan dose by 20%.

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

Tiredness, diarrhoea and abdominal pain, acute cholinergic syndrome, nausea and vomiting, sore mouth/stomatitis, poor appetite, myelosuppression and thrombocytopenia, hand foot syndrome, cardiotoxicity (including coronary artery spasm, angina and tachycardia), ocular toxicity (excessive lacrimation, visual change, photophobia), infusion reactions, veno-occlusive disease, hair loss, neurotoxicity, ovarian failure/infertility, transient cerebellar syndrome, confusion

Significant drug interactions

– for full details consult product literature/ reference texts

Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Capecitabine enhances the anticoagulant effects of warfarin. Avoid combination. Switch to low molecular weight heparin if possible.

Avoid concomitant use of capecitabine and allopurinol

Exposure to irinotecan may be increased by strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin) and reduced by strong CYP3A4 inducers (e.g. rifampicin, carbamazepine)

References

Campto SPC – accessed 9/9/2020 https://www.medicines.org.uk/emc/product/2213/smpc
Xeloda SPC – accessed 9/9/2020 https://www.medicines.org.uk/emc/product/1319/smpc

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: Jan 2021
Review: Jan 2023
VERSION: 9