Capecitabine concurrent with radiotherapy

Indication
Pre-operative use in rectal cancer to down stage the tumour prior to surgery

ICD-10 codes
Codes with a prefix C20

Regimen details

Days	Drug	Dose	Route
1-35*	Capecitabine	825mg/m^2 bd	PO

*Taken on radiotherapy days ONLY (usually Monday to Friday)
In elderly (≥70 years) or frail patients consider reducing starting dose to 625mg/m^2 BD.

Cycle frequency
As above

Number of cycles
One cycle only

Administration
Capecitabine is available as 150mg and 500mg tablets.
Tablets should be taken after food and swallowed whole with a glass of water.

Pre-medication
Nil

Emetogenicity
This regime has moderate-low emetogenic potential

Additional supportive medication
Loperamide if required
Topical emollients to prevent PPE
H2 antagonist or proton pump inhibitor if required

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Random glucose	14 days
HbA1c	3 months

DPYD mutation analysis	none
Hepatitis B serology (HBsAg, HBcAb)	none

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST) weekly

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	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN

Dose modifications

Once a dose has been reduced it should not be increased at a later time.

Haematological toxicity

If neutrophils <1 x 10^9/L and/or platelets <75 x 10^9/L delay 1 week (continue radiotherapy). If FBC recovered after 1 week then restart at 75% dose.

If further delays are needed then consider further dose reduction or discontinue capecitabine (consultant decision).

Renal impairment

CrCl (mL/min)	**Capecitabine dose**
≥ 50	100%
30-49	75% (with close monitoring)
<30	Contraindicated

Hepatic impairment

Lack of information available. In patients with mild to moderate hepatic dysfunction (bilirubin <3 x ULN and/or AST/ALT <5 x ULN) probably no dose reduction necessary, consultant decision.

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.

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.

For patients with heterozygous DPYD genotypes national guidance should be followed for recommended starting dose. Dose increment weekly from week 3 of radiotherapy if tolerated, increased to maximum of the target dose for genotype as recommended in the guidance.

Patients with compound heterozygous or homozygous genotypes should not receive fluoropyrimidine therapy with radiotherapy.

dpd-testing-ukcb-july-2020-final.pdf (theacp.org.uk)

Other toxicities

Other toxicities should be managed by symptomatic treatment and/or dose modification (e. by treatment interruption or undertaking a dose reduction).
Once the dose has been reduced, it should not be increased at a later time.

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		

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

Serious side effects

Myelosuppression
Infertility
Allergic reactions
Neurotoxicity
Nephrotoxicity
Coronary artery spasm*

*Coronary artery spasm is a recognised complication of fluoropyrimidine 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
Fatigue
Dyspnoea

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.
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

If capecitabine doses are omitted due to capecitabine-related toxicity, radiotherapy should continue. Once radiotherapy competed, capecitabine treatment should not continue, even if the patient has not taken the full course.

References

Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 5 May 2022
Summary of Product Characteristics (Capecitabine) accessed 5 May 2022 via www.medicines.org.uk
Personalised Medicine Approach for Fluoro-pyrimidine-based Therapies. UK Chemotherapy Board July 2020 accessed 5 May 2022 via dpd-testing-ukcb-july-2020-final.pdf (theacp.org.uk)

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

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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