Mitomycin C and capecitabine concurrent with radiotherapy

Indication

Anal cancer
Vulval cancer

Regimen details

Regimen 1- for use concurrent with 5 ½ weeks radiotherapy (28 fractions)

D1	Mitomycin	12mg/m^2	IV bolus	
Start Day 1: taken for the duration of radiotherapy but taken on days of radiotherapy only	Capecitabine	825mg/m^2 bd	PO	Supply 28 days (56 doses)

Mitomycin Maximum dose 20mg

Regimen 2- for use concurrent with 4 ½ weeks of radiotherapy (23 fractions)

D1	Mitomycin	12mg/m^2	IV bolus	
Start Day 1: taken for the duration of radiotherapy but taken on days of radiotherapy only	Capecitabine	825mg/m^2 bd	PO	Supply 23 days (46 doses)

Mitomycin Maximum dose 20mg

Cycle frequency

Single cycle

Number of cycles

One

Administration

Mitomycin C is given as a bolus injection and is vesicant, avoid extravasation
Patient must be able to comply with oral chemotherapy regimen. Tablets should be taken after food and swallowed whole with a glass of water.

Pre-medication

Antiemetics as per local policy

Emetogenicity

This regimen has a low emetogenic potential

Additional supportive medication

Loperamide if required.
Metoclopramide 10mg tds prn.
Topical emollients to prevent PPE

Extravasation

Mitomycin is a vesicant

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs (including AST)	14 days
Bone profile	14 days
CEA	14 days
DPYD mutation testing	none
Hepatitis B serology (HBsAG, HBcAb)	none
HIV serology (for squamous anal cancers)	none
HbA1c	3 months
Random glucose	14 days
ECG	28 days

Dose modifications

Renal impairment

CrClearance (mL/min)	Mitomycin C
≥30	100% dose
<30	Omit
CrClearance (ml/min)	**Capecitabine**
>50	100% dose
30-50	75% dose
<30	Omit

Hepatic impairment

Dose modification may be required. Capecitabine and Mitomycin have not been studied in severe hepatic dysfunction

Mitomycin C	Bilirubin 1.5-3 x ULN or ALT / AST 1.5-3 x ULN	Consider 50% dose reduction
	Bilirubin > 3 x ULN or ALT / AST >3 x ULN	Omit
Capecitabine	Bilirubin 1.5-3 x ULN or ALT / AST 1.5-3 x ULN	Consider 50% dose reduction
	Bilirubin > 3 x ULN or ALT / AST >3 x ULN	Omit

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.

If DPYD report advises starting at 50% dose then to give 50% dose weeks 1 and 2, for twice weekly FBC. If any concern about DPYD related toxicity, then either discontinue or continue at 50%. If no evidence of DYPD related toxicity, then escalate dose to 75% for the remaining treatment and continue with twice weekly FBC. If any concerns discuss with consultant.

Standard limits for administration to go ahead (Day 1)

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

Investigation	Limit
Haemoglobin	≥10 g/dL
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 50 mL/min (see dose modifications below)
Bilirubin	≤ 1.5 x ULN
AST/ALT	< 1.5 x ULN

Investigations –weekly during treatment

FBC, U&Es and LFTs (including AST), calculated creatinine clearance, random glucose

Standard limits for treatment to continue

Investigation	Limit
Haemoglobin	≥10 g/dL
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L
Creatinine clearance	≥ 50 mL/min (see dose modifications below)
Bilirubin	≤ 1.5 x ULN
AST/ALT	< 1.5 x ULN

Guidance for dose modifications for chemotherapy and radiotherapy toxicities

- **Haematological**

HAEMATOLOGICAL			
CTCAE Grade	**Description**	**Capecitabine or 5FU**	**Radiotherapy**
1	Haemoglobin ≥10.0g/dL – LLN	Full dose (100%)	Continue
	Neutrophils ≥1.5 x 10^9/L – LLN	Full dose (100%)	Continue
	Platelets ≥75 x 10^9/L - LLN	Full dose (100%)	Continue
2	Haemoglobin <10.0 - 8.0g/dL	Full dose (100%)	Continue
	Neutrophils <1.5 – 1.0 x 10^9/L	Full dose (100%)	Continue
	Platelets <75 – 50 x 10^9/L	Interrupt until resolved to Grade 0 or 1 then continue at full dose (100%)	Continue
3*	Haemoglobin <8.0g/dL transfusion indicated.	Interrupt until resolved to Grade 0 or 1 then **Continue** at full (100%) dose	Continue. Transfuse in the next 24-48 hours.
	Neutrophils <1.0 – 0.5 x 10^9/L.	Interrupt until resolved to Grade 0 or 1 th Continue at full (100%) dose	Continue. Prophylactic Antibiotics (eg. Ciprofloxacin 500mg BD)
	Platelets <50 – 25 x 10^9/L	Interrupt until Grade 0 or 1, then resume at 75% dose	Continue. Consider platelet transfusion if clinically indicated (eg. bleeding).
If patient is neutropenic and has sepsis,		Stop permanently	Continue, provided patient haemodynamically stable and considered fit for treatment.
4*	Haemoglobin - Life threatening consequences; urgent intervention indicated	Discuss with t **Consultant**	Interrupt until Grade 2. Emergency transfusion, consider other causes of falling Hb (eg. bleeding).
	Neutrophils < 0.5 x 10^9/L	Stop permanently	Continue. Prophylactic Antibiotics (eg. Ciprofloxacin 500mg BD)
	Platelets < 25 x 10^9/L	Stop permanently	Interrupt until Grade 2. Consider platelet transfusion. Consider other causes of thrombocytopenia.

In presence of G3/4 haematological toxicity blood tests should be performed at a minimum of twice a week depending on clinical circumstances.

- **Renal impairment**

IMPAIRED RENAL FUNCTION	
GFR Calculated as per Cockroft and Gault calculation (Appendix E)	**Capecitabine or 5FU**
≥50 mL/min	Full dose (100%)
30 – 49 mL/min	75% dose
<30 mL/min	Stop permanently

- **Hepatic impairment**

IMPAIRED LIVER FUNCTION		
CTCAE Grade	**Description**	**Capecitabine or 5FU**
2	Elevated bilirubin* >1.5 – 3.0 x ULN	75% dose
3	Elevated bilirubin >3.0 – 10 x ULN	Stop permanently
≥2	ALT or AST > 3 x ULN	Interrupt until Grade 1 then restart at 75% dose

- **Other toxicities**

DIARRHOEA			
CTCAE Grade	**Description**	**Capecitabine or 5FU**	**Radiotherapy**
1	Increase of < 4 stools per day **over baseline**; mild increase in ostomy output compared to baseline	Full dose (100%)	Continue
2	Increase of 4 – 6 stools per day **over baseline**; moderate increase in ostomy output compared to baseline; Moderate cramping	Continue as long as patient considered fit for treatment.	Continue Manage as clinically indicated (eg. Loperamide, ensure oral hydration maintained)
3	Increase of > 7 stools per day **over baseline**; severe increase in ostomy output compared to baseline; limiting self-care ADL; Severe cramping or peritonism (localised guarding on abdominal examination)	Interrupt until Grade 0 – 1, ≤ 6 mg loperamide per 24 hours required, and patient considered fit, then recommence at 75% dose.	For incontinence - continue. Management as per clinically indicated (eg. loperamide, codeine, iv hydration, monitor renal function), consider inpatient management for treatment and support. Check that stoma is avoided from radiotherapy portals. **Do not treat if localised peritonism**
4	Life threatening consequences; urgent intervention indicated	Stop permanently.	Interrupt until resolved to Grade 2. Reassess daily

ORAL MUCOSITIS			
CTCAE Grade	Description	Capecitabine or 5 FU	
		1st appearance	2nd appearance
1	Asymptomatic or mild symptoms; intervention not indicated	Full dose (100%)	Full dose (100%)
2	Moderate pain; not interfering with oral intake; modified diet indicated	Interrupt until Grade 0 – 1, then resume at 75% dose	Stop permanently
3	Severe pain; interfering with oral intake	Interrupt until Grade 0 – 1, then resume at 50% dose	Stop permanently
4	Life-threatening consequences; urgent intervention indicated	Stop permanently	

RADIATION DERMATITIS			
CTCAE Grade	Description	Capecitabine or 5FU	Radiotherapy
1	Follicular, faint or dull erythema/epilation/dry desquamation/ decreased sweating.	Full dose (100%)	Continue
2	Tender or bright erythema, patchy moist desquamation/moderate oedema.	Full dose (100%)	Continue. Manage skin toxicity as clinically indicated (eg. aqueous cream or hydrocortisone on intact skin, hydrogel and non-adhesive / silicone based dressings as appropriate on areas of desquamation).
3	Confluent, moist desquamation other than skin folds, pitting oedema.	Full dose (100%)	Continue. Manage skin toxicity as per local protocol (eg. aqueous cream on intact skin, hydrogel and non-adhesive / silicone based dressings as appropriate on areas of desquamation). Manage pain with paracetamol, weak analgesics using WHO pain control ladder
4	Ulceration, haemorrhage, necrosis.	Stop permanently	Interrupt until Grade 3.

Haemolytic Uraemic Syndrome (HUS)	Microangiopathic haemolytic anaemia, renal failure, thrombocytopenia and hypertension. More common with cumulative doses of mitomycin C >36mg/m^2 and can occur several months after treatment If suspected test for red call fragmentation Discuss with renal team Consider prednisolone 30mg OD for 7 days to prevent worsening haemolysis

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.

OTHER NON-HAEMATOLOGICAL TOXICITY		
CTCAE Grade	**1st appearance**	**2nd appearance**
1	- Full dose (100%) chemotherapy with supportive treatment - Continue radiotherapy	- Full dose (100%) chemotherapy with supportive treatment - Continue radiotherapy
2	- Interrupt chemotherapy treatment until resolved to Grade 0-1, then continue at full dose (100%) with prophylaxis where possible - Continue radiotherapy	- Interrupt chemotherapy treatment until resolved to Grade 0-1, then restart at 75% dose - Continue radiotherapy
3	- Interrupt chemotherapy treatment until resolved to Grade 0-1, then consider restart at 75% dose if deemed suitable by treating clinician - Please contact **Consultant** for advice on radiotherapy interruptions if ≥G3 toxicity excluding PPE, diarrhoea, mucositis and deranged liver function tests, haematological, radiation dermatitis or vomiting.	- Discontinue chemotherapy permanently
4	- Discontinue chemotherapy permanently - Please contact **Consultant** for advice on radiotherapy interruptions if ≥G3 toxicity excluding PPE, diarrhoea, mucositis and deranged liver function tests, haematological, radiation dermatitis or vomiting.	

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Sepsis
Infertility
Nephrotoxicity
Hepatoxicity
Cardiac disorders
Haemolytic Uraemic syndrome
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.

- **Other side effects**

Headache
Dizziness
Dysgeusia
Transient cerebellar syndrome
Confusion

Sore mouth, nausea/sickness, pain in abdomen, diarrhoea, skin reaction, conjunctivitis, myelosuppression, neutropenia, thrombocytopenia, cardiac toxicity, ocular toxicity, interstitial lung disease, HUS, diarrhoea and constipation, fatigue, mild alopecia

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.
Tamoxifen: Increased risk of HUS with concomitant use with mitomycin

Additional comments

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

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.

References

- Summary of Product Characteristics (Capecitabine) accessed 25th September 2024 via www.medicines.org.uk
- Summary of Product Characteristics (Mitomycin) accessed 25th September 2024 via www.medicines.org.uk
- Personalised Medicine Approach for Fluoro-pyrimidine-based Therapies v2 Sept 2024 accessed 6th March 2025 via https://www.uksactboard.org/_files/ugd/638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf
- PLATO (Personalising Anal cancer Radiotherapy dose) trial Protocol Version 7.0 September 2022 accessed 19th March 2025

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

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: September 2025
Review: September 2027
VERSION: 6