SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Mitomycin C and Capecitabine with XRT (MMC Capecitabine XRT)

PROTOCOL REF: MPHAMCXGA
Version No.3.0

Approved for use in:

- Chemo-radiation to Localised / Adjuvant Squamous cell anal carcinoma
- Chemo-radiation to Advanced Squamous cell anal carcinoma for local control

Dosage:

Drug	Dose	Route	Frequency
Mitomycin C	**12mg/m^2 (max dose 20mg)**	IV	Day 1
Capecitabine	825 mg/m^2 BD (Monday to Friday) **on radiotherapy treatment days**.	PO	Monday to Friday on 28 radiotherapy treatment days over 5 and a half weeks.

Single cycle only (with concurrent radiotherapy)
**Mitomycin C and Capecitabine to be started on Day 1 of radiotherapy

Emetogenic risk:

Low emetogenic

Supportive treatments:

Metoclopramide 10mg up to three times a day when required

Loperamide 4mg initially, then 2mg after each loose stool

Extravasation risk:

Mitomycin C - Vesicant.

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone**	8mg	Oral	N/A
1	**Mitomycin C**	12mg/m^2 (maximum dose 20mg)	IV	IV Bolus in sodium chloride 0.9% over 10 min
D1 to D5, D8 to D12, D15 to D19, D22 to D26, D29 to D33, D36 to D38 **On Radiotherapy Days**	**Capecitabine**	825mg/m^2 twice daily Monday to Friday on 28 radiotherapy treatment days for five and a half weeks	PO	N/A

Notes:

Maximum cumulative Mitomycin dose is 28mg/m^2 or 56mg total

Counselling points:

Capecitabine

Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias or taking high dose aspirin or coumarin anticoagulants

Be aware of infusion related allergic reactions

Teratogenic risk – advice on contraception

Capecitabine tablets are available in 150mg and 500mg strengths

Tablets should be taken 12 hours apart, morning and evening. Swallow whole with water within 30 minutes of a meal. Do not add doses missed due to toxicity onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day.

Take missed doses if remembered within 2 hours of the normal scheduled time. Otherwise continue with the next scheduled dose. Do not double up missed doses.

In case of swallowing difficulties the tablets may be dissolved in 200ml warm water. Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only.

Mitomycin

Given via fast running infusion of 0.9% NaCl

Interactions:

Capecitabine
• Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully • Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH • Sorivudine and analogues – Potentially fatal interaction – avoid completely • Cimetidine, metronidazole and interferon may increase the plasma level of capecitabine, thereby increasing the toxicity of caepcitabine. • Capecitabine enhances the action of other cytostatic drugs and irradiation therapy. • Avoid live vaccines. • Alcohol – please advise to stop drinking whilst on chemotherapy • Enoxaparin / Dalteparin – monitor for bleeding signs

Main toxicities:

Mitomycin-C	
Blood and lymphatic system disorders	Bone marrow suppression, leukopenia, thrombocytopenia
Respiratory, thoracic and mediastinal disorders	Interstitial pneumonia, dyspnoea, cough, shortness of breath
Gastrointestinal disorders	Nausea, vomiting
Skin and subcutaneous tissue disorders	Exanthema, allergic skin rash, contact dermatitis, palmar-plantar erythema
Renal and urinary disorders	Renal dysfunction, increase in serum creatinine, glomerulopathy, nephrotoxicity

General disorders and administration site conditions	Following extravasation: Cellulitis, tissue necrosis

Capecitabine

- Neutropenia, thrombocytopenia, anaemia, leukopenia
- Mucositis, Stomatitis
- Nausea, vomiting, diarrhoea, abdominal pain,
- Cardiac Ischaemia, ECG abnormalities
- Conjunctivitis
- Infections, immunosuppression
- Bronchospasms, epistaxis
- Palmar-plantar syndrome, alopecia
- DPD deficiency – can lead to life threatening toxicity

DPYD

Reaction characteristics:

- **stomatitis, diarrhoea, mucosal inflammation, neutropenia, neurotoxicity**

Toxicity usually occurs during the first cycle of treatment

Normal	100% dose
Intermediate metaboliser (Decreased DPD activity)	Reduce dose by 50%. Dose increment at clinician discretion
Poor metaboliser (Complete DPD deficiency)	Avoid – toxicity can be fatal

Antidote: Uridine Triacetate (refer to Policies & Documents - Uridine Triacetate for Patients with Early-Onset Severe Toxicities Following 5-Fluorouracil or Capecitabine - All Documents (sharepoint.com)

Investigations and treatment plan:

	Cycle 1						Comments
	Pre	Day 1	Day 8	Day 15	Day 22	Day 29	
Informed Consent	x						
Clinical Assessment	x		x	x	x	x	Review after completion of 28# RT: - weekly for 2 weeks, - clinic review on 6th week, - MRI scan on 3rd month, - CT + MRI on 6th month
SACT Assessment	x		x	x	x	x	
FBC	x		x	x	x	x	Weekly
U&E & LFT	x		x	x	x	x	Weekly
CrCL (Cockroft & Gault formula)	x						
Dihydropyrimidine dehydrogenase (DPD) deficiency test	x						This test is required for every patient newly started on capecitabine or fluorouracil. The result MUST be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary.
Height and weight recorded	x						

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC <1.0 x 10^9/L	Plt <100x 10^9/L

If platelets or Absolute Neutrophil Count (ANC) still below required levels for treatment after week 2, delay treatment again and patient will need to be assessed and consideration given for a chemotherapy dose reduction. Refer to consultant if in doubt.

Dosing in renal impairment

Mitomycin – C	**Creatinine Clearance (ml/min)**	**Mitomycin-C**
	Above 30	No dose adjustment
	Below 30	Not recommended

Capecitabine	**Creatinine Clearance (ml/min)**	**Capecitabine**
	Above 30	No dose adjustment
	Below 30	Omit

Dosing in hepatic impairment

Note that significant impairment may be a sign of disease progression and require cessation or change of treatment. Always discuss deteriorating organ function with consultant.

Mitomycin – C	Bilirubin > 3 x ULN or ALT / AST >2.5 x ULN, consider 50% dose reduction
Capecitabine	If Bilirubin > 3 x ULN or ALT/AST > 2.5 x ULN then omit capecitabine until liver function recovers – refer to consultant before dose reduction

Non- Haematological toxicity management:

Mitomycin-C

Haemolytic Uremic Syndrome	Monitor renal function / urine dipstick carefully and request red cell fragments on peripheral blood films if in doubt. It is associated with prolonged course lengths and cumulative doses above 50mg/m^2 and can occur several months after treatment

Capecitabine

Diarrhoea

Diarrhoea can be secondary to radiotherapy. Discuss with team prior to dose reduction.

Loperamide at standard doses – ensure maximum dose reached, codeine may be added – see table below for dose reductions

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None or no change from normal	Increase of up to 3 bowel movements a day over pre-treatment normal or mild increase in ostomy output	Increase of up to 4-6 episodes a day or moderate increase in ostomy output or nocturnal movement or moderate cramping	Increase of up to 7-9 episodes a day or severe increase in ostomy output or incontinence / severe cramping / bloody diarrhoea	Increase >10 episodes a day or grossly bloody diarrhoea

Stomatitis

Regular mouthwashes (water, saline or non alcoholic proprietary brand), brush gently with a soft brush, adequate pain relief, nutritional support in severe cases – see below for dose reductions.

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic, mild symptoms	Moderate pain or ulcer that does not interfere with oral intake, modified diet indicated	Severe pain, interfering with oral intake	Life threatening conditions, requires urgent intervention

Palmar plantar erythema (PPE) or hand foot syndrome

Manage as per trust policy, withhold treatment until resolved to grade 1, dose reductions as per table below.

Sore eyes / Conjunctivitis

Eye drops for symptomatic treatment such as hypromellose 0.3% – avoid antimicrobial eye drops unless indicated for infective conjunctivitis

Chest Pain / coronary artery spasm	Stop capecitabine, standard angina investigations, and perform emergency medical assessment. If occurs on the day unit during administration, request for urgent medical review (SpR in CCC-L, and MET team in our chemotherapy hubs) If occurs at home, go to the local A&E. Please inform tumour site consultant after.

Haematological and Non-haematological dose adjustment guidelines according to Common Toxicity Criteria

	Non haematological toxicities **(diarrhoea, stomatitis, PPE)**			
Grade	0-1	2	3	4
1st occurrence	100%	80%	50%	Stop treatment
2nd occurrence	80%	70%	50%	Stop treatment
3rd occurrence	50%	50%	50%	Stop treatment

References:

1. Summary of Product Characteristics, Electronic Medicines Compendium, Mitomycin Available from: Last updated March 2022
2. Summary of Product Characteristics, Electronic Medicines Compendium, Capecitabine. Available from: Capecitabine 500 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Last updated: Feb 2023
3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
4. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27
5. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; **20:** e201–08.
6. MHRA – DPD testing 5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity - GOV.UK (www.gov.uk)

Circulation/Dissemination

Date added into Q-Pulse	27th February 2024
Date document posted on the Intranet	NA

Version History

		Author name and designation	Summary of main changes
January 2024	3.0	Aaron Teoh – Advanced Clinical Pharmacist	• Updated to new template to ver 2.0 • Updated Approval use section • Updated dosage section, clarified dosing frequency and starting date • Updated emetogenic risk • Standardised haematological toxicity parameters • Updated mitomycin and capecitabine Dosing in Hepatic Impairment as per CTCAE v5.0 • Standardised Haematological and Non-haematological dose adjustment guidelines dose reduction as per Grading • Added Grading for diarrhoea and stomatitis as per CTCAE criteria