SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Mitomycin C and Fluorouracil

Anal Cancer

PROTOCOL REF: **MPHAMCFLGA**
Version No. 2.0

Approved for use in:

Advanced / Metastatic Squamous cell anal carcinoma

Dosage:

Drug	Dosage	Route	Frequency
Mitomycin C	7 mg/m^2	IV	Every 42 days
Fluorouracil	1000mg/m^2 daily for 4 days	IV	Days 1 – 4 and days 22 – 25 of each cycle

For maximum of 4 cycles, each cycle is 42-day.

Administration & Counselling Points:

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

Teratogenic risk – advice on contraception

Emetogenic risk:

Moderate

Supportive treatments:

Metoclopramide 10mg oral tablets, up to 3 times a day or as required

Extravasation risk:

Mitomycin-C – vesicant

Fluorouracil - Irritant

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

Treatment schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	8mg	Oral	N/A
1	Mitomycin C	7mg/m^2	IV	IV bolus in sodium chloride 0.9% over 10 mins
1 to 4	Fluorouracil	1000mg/m^2 daily for 4 days	IV	Via LV2 burgundy ambulatory infusion device in sodium chloride 0.9% over 96hrs at 2ml/hr
22 to 25	Fluorouracil	1000mg/m^2 daily for 4 days	IV	Via LV2 burgundy ambulatory infusion device in sodium chloride 0.9% over 96hrs at 2ml/hr

Notes:

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

Care with patients on coumarin anticoagulants – monitor INR closely, consider LMWH

Sorivudine and analogues – Potentially fatal interaction – avoid completely

For severe reactions, discuss with Consultant before continuing with treatment.

Interactions:

Fluorouracil
• 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 5-fluorouracil, thereby increasing the toxicity of 5-fluorouracil. • Fluorouracil 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

Fluorouracil
Neutropenia, thrombocytopenia, anaemia, leukopenia
Mucositis, 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

Investigations and treatment plan:

	Cycle 1				Subsequent cycles			Comments
	Pre	**Day 1**	**Day 22**	**Day 29**	**Day 1**	**Day 22**	**Day 29**	
Clinical assessment	X				X			Every 3 months and as clinically indicated
SACT Assessment	X	X	X		X	X		Every cycle
FBC	X		X	X	X	X	X	Every cycle
U&E & LFT	X		X	X	X	X	X	Every cycle
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.
Informed Consent	X							
Weight recorded	X	X			X	X		

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100x 10^9/L

Delay 1 week on day 1 if-

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

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Dosing in renal and hepatic impairment:

Calculate CrCl using Cockroft and Gault formula at baseline and before each cycle and adjust dose according to table:

Renal

Creatinine Clearance (mL/min)	**Fluorouracil Dose**
≥ 30	Full dose
< 30	Give 75%

Creatinine Clearance (ml/min)	**Mitomycin-C**
Above 10	No dose adjustment
Below 10	75% dose

Hepatic

Fluorouracil	
Bilirubin 1.5 to 3 x ULN ALP>5 x ULN	100%
Bilirubin > 3 x ULN	50%
Mitomycin-C	

	Bilirubin > 3 x ULN or ALT / AST >2.5 x ULN	Consider 50% dose reduction

Note that significantly impaired hepatic function might be a sign of disease progression and require cessation or change of treatment.

Always discuss deteriorating organ function with consultant

Non- Haematological toxicity:

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. Has been known at shorter and lower doses

Fluorouracil	
Chest pain, coronary artery spasm	Stop fluorouracil, standard angina investigations, stop 5FU immediately, 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.
Stomatitis	If mouth ulcers or > grade 2 symptoms develop treat symptomatically, delay treatment until resolved to grade 1 and reduce fluorouracil doses by 20%. (See table)

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

Diarrhoea	Treat diarrhoea between cycles symptomatically.

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If diarrhoea has not resolved by next cycle delay treatment by 1 week.
If diarrhoea remains troublesome or > 1 week:

Delay is required reduce both fluorouracil bolus and infusion doses by 20% and continue at the lower dose unless further toxicity occurs (See table)
<table>
<tr><th>Grade 0</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td>None or no change from normal</td><td>Increase of up to 3 bowel movements a day over pre-treatment normal or mild increase in ostomy output</td><td>Increase of up to 4-6 episodes a day or moderate increase in ostomy output or nocturnal movement or moderate cramping</td><td>Increase of up to 7-9 episodes a day or severe increase in ostomy output or incontinence / severe cramping / bloody diarrhoea</td><td>Increase >10 episodes a day or grossly bloody diarrhoea</td></tr>
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<tr><td>Palmar-Plantar Erythrodysesthesia (PPE)</td><td>Treat symptomatically, delay treatment until resolved to grade 1.

Reduce fluorouracil doses (bolus and infusion) by 20% for subsequent doses if persistent troublesome PPE. (See table)

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Fluorouracil dose reductions for non haematological toxicity

	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

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)

References:

1. Summary of Product Characteristics, Electronic Medicines Compendium, Mitomycin, https://www.medicines.org.uk/emc
2. Summary of Product Characteristics, Electronic Medicines Compendium, Fluorouracil, https://www.medicines.org.uk/emc/medicine/636
3. BNF available via: https://bnf.nice.org.uk/
4. Northern Cancer Alliance, Anti-emetic Guidelines for Chemotherapy Induced Nausea and Vomiting. North of England Cancer Network (northerncanceralliance.nhs.uk)
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)
7. ACT II trial (2013)

Circulation/Dissemination

Date added into Q-Pulse	27th February 2024
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
February 2024	2.0	**Aaron Teoh – Advanced Cancer Pharmacist**	• New format • Updated indication • Updated interactions • Updated main toxicities, included mitomycinC • Updated renal and hepatic impairment • Added Non Haematological toxicity for Mitomycin C • Added 5FU dose modification table • Added DPYD section