Systemic Anti Cancer Treatment Protocol

Mitomycin C and Capecitabine with XRT Anal Cancer (MMCAP anal XRT)

PROTOCOL REF: MPHAMCXGA
(Version 1.0)

Approved for use in:

- Localised squamous carcinoma of the anus

Dosage:

Drug	Dosage	Route	Frequency
Mitomycin C	12 mg/m^2 (maximum dose 20mg)	IV	Day 1
Capecitabine	825 mg/m^2 BD for 5 days (Monday to Friday) for five weeks.	PO	Take Monday to Friday on radiotherapy treatment days for five weeks.

For a single cycle only with concurrent radiotherapy

Supportive treatments:

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

Loperamide 4mg initially, then 2mg after each loose stool (maximum 16mg in 24hrs)

Extravasation risk:

Mitomycin-C – vesicant

Refer to Clatterbridge Policy 'Prevention and Management of Extravasation Injuries' for further guidance.

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	8mg	Oral	N/A
1	Mitomycin C	12mg/m^2	IV	IV bolus in sodium chloride 0.9% over 10 mins
1 to 33	Capecitabine	825mg/m^2 twice daily Monday to Friday on radiotherapy treatment days only for 5 weeks	PO	N/A

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

Caution in patients with pre-existing coronary heart disease, angina pectoris, arrhythmias.

Medical/Nursing review as per patient management plan

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

Counselling points:

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

Drug Interactions

Allopurinol – reduced efficacy of capecitabine – avoid

Clozapine – additive risk of agranulocytotis

Folic acid – increased risk of side effects of capecitabine, avoid if possible – discuss with pharmacy

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

Main Toxicities:

Mitomycin-C – myelosuppression, haemolytic uremic syndrome, pulmonary toxicity, diarrhoea, constipation, stomatitis, cholecyctitis, jaundice, acute renal failure and proteinuria. Haemolytic Uraemic Syndrome consists of microangiopathic haemolytic anaemia, renal failure thrombocytopaenia, and hypertension. Patients are at greater risk if they have renal failure, evidence of red cell fragmentation and if they have received several courses of treatment with cumulative doses of Mitomycin-C >36mg/m^2. Where suspected, test for red cell fragmentation. HUS may be treated with Prednisolone 30mg once daily for one week to prevent worsening haemolysis. Patient should be discussed with renal team.

Capecitabine - Myelosuppression, diarrhoea, Palmar Plantar Erythema (PPE or hand-foot syndrome), stomatitis, fatigue, asthenia, anorexia, cardiotoxicity (uncommon), ovarian failure/infertility, increased renal dysfunction on those with pre-existing compromised renal function, and thrombosis/embolism.

DPD deficiency – leads to severe early capecitabine toxicity, affects approximately 3% of population, may be life threatening.

Investigations and treatment plan

	Cycle 1					
	Pre	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**
Clinical Assessment	x		x	x	x	x
SACT Assessment	x					
FBC	x		x	x	x	x
U&E & LFT	x		x	x	x	x
CrCL (Cockroft & Gault formula)	x					
CT scan	x					
Informed Consent	x					
Height recorded						
Weight recorded	x					
Urine dipstick for protein / RBC	x					

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Discuss with consultant oncologist if blood results are below these recommended limits.

Renal impairment:

CrCl (mL/min)	Mitomycin-C
Above 60	100% dose
10 – 60	80% dose
Below 10	60% dose

CrCl (mL/min)	Capecitabine
Above 30	100%
Below 30	Omit

Creatinine Clearance (CrCl) calculated according to Cockcroft & Gault formula:

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

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. (Note. ULN = Upper limit of normal range)

Mitomycin-C
Clinical decision when AST levels > 2 x ULN. Clearance is primarily by metabolism in the liver, with approximately 10% of a dose excreted unchanged in the urine.

Capecitabine
If Bilirubin > 3 x ULN or ALT/AST > 2 x ULN then omit capecitabine until liver function recovers – refer to consultant

Non-haematological toxicity

Mitomycin

Haemolytic Uremic Syndrome	This a complication of mitomycin-C. 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

Capecitabine

Diarrhoea	Loperamide at standard doses – ensure maximum dose reached, codeine may be added – see table below for dose reductions
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.
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 eyedrops unless indicated for infective conjunctivitis
Chest Pain / coronary artery spasm	Stop capecitabine, standard angina investigations, refer to consultant, if symptoms persist stop capecitabine permanently

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

Toxicity grades / Haematological parameter	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
• *Grade 1*	Maintain dose level	Maintain dose level
• *Grade 2*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• *Grade 4*		
-1st appearance	Discontinue permanently *Or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

References:

Summary of Product Characteristics, Electronic Medicines Compendium, Mitomycin, www.medicines.org.uk/emc/medicine/26917

Summary of product characteristics, Electronic Medicines Compendium, Xeloda®, https://www.medicines.org.uk/emc/medicine/4619