mitoMYcin and Capecitabine Chemoradiation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of anal canal carcinoma	C21	00727a	mitoMYcin: N/A Capecitabine: N/A

* This is for post 2012 indications only.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

mitoMYcin is administered on days 1 and 29.
Capecitabine is administered on days 1-5 (week 1), 8-12 (week 2), 15-19 (week 3), 22-26 (week 4), 29-33 (week 5) and 36-40 (week 6) concurrently with radiotherapy for 1 cycle.
One cycle is equal to 42 days.

Note: Capecitabine treatment is completed on the last day of radiotherapy.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Cycle
1, 29	mitoMYcin	10mg/m^2 (Cap dose at 20mg)	IV bolus (via fast running NaCl 0.9% infusion)	For one cycle only
1-5, 8-12, 15-19, 22-26, 29-33, 36-40	Capecitabine	825mg/m^2 twice daily [a,b,c]	PO with food	For one cycle only
[a]The dose to be administered should consider the available tablet strengths. Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine Here. Tablets should be swallowed whole with plenty of water within 30 minutes of eating. Tablets should not be crushed or cut. (total daily dose = 1650mg/m^2)				
[b]Starting dose of capecitabine 500mg/m^2 twice daily may be considered for patients aged 71 years and above and/or if there is a significant intercurrent illness.				
[c] See dose modifications section for patients with identified partial Dihydropyrimidine dehydrogenase (DPD) deficiency.				

ELIGIBILITY:

- Indication as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to mitoMYcin, capecitabine or any of the excipients
- Known complete Dihydropyrimidine dehydrogenase (DPD) deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- Severe hepatic or renal impairment

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile weekly throughout treatment

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Consider a reduced starting dose in patients with identified partial DPD deficiency.
    - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Haematological:

Table 1: Dose modification of capecitabine in haematological toxicity

ANC ($x 10^9/L$)		Platelets ($x 10^9/L$)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
≥ 1.5	and	≥ 75	100%	100%	100%	100%
1-1.49	or	50–74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5-0.99	or	25-49.9	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
< 0.5	or	< 25	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

*Delay until ANC ≥ 1.5x 10^9/L and platelets ≥ 75x10^9/L

Renal and Hepatic Impairment:

Table 2: Dose Modification of mitoMYcin and Capecitabine in Renal and Hepatic Impairment

Drug	Renal Impairment		Hepatic Impairment*	
Capecitabine	**CrCl (mL/min)**	**Dose**	No dose adjustment is needed	
	51-80	No dose adjustment is needed		
	30-50	75% of the original dose		
	<30	Not recommended		
	Haemodialysis	Not recommended		
mitoMYcin	**CrCl (mL/min)**	**Dose**	**Mild –Moderate**:	No need for dose adjustment is expected
	≥30	no need for dose adjustment is expected		
	<30	Not recommended	**Severe**:	Consider 50% of the original dose
	Haemodialysis	Not recommended due to nephrotoxicity		
Renal and hepatic dose modifications for capecitabine and mitoMYcin: Giraud at al 2023 *Reference Table 6 for dose modification of capecitabine in treatment related hepatotoxicity.				

Management of adverse events:

Table 3 shows the recommended dose modifications of capecitabine for those toxicities which are not individually specified:

Table 3: Capecitabine dose reduction schedule based on toxicity (Any)

Toxicity grades*	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 permanently	
Grade 3		
• 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	
Grade 4		
• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
• 2nd appearance	Discontinue permanently	
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy.		

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 4: Dose Modification of capecitabine for diarrhoea

Grade	Diarrhoea	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
0-1	Increase of 2 to 3 stools/day or nocturnal stools	Maintain dose level	Maintain dose level
2	Increase of 4 to 6 stools/day or nocturnal stools		
	• 1st appearance	Interrupt until resolved to grade 0-1	100%
	• 2nd appearance		75%
	• 3rd appearance		50%
	• 4th appearance	Discontinue permanently	
3	Increase of 7 to 9 stools/day or incontinence		
	• 1st appearance	Interrupt until resolved to grade 0-1	75%
	• 2nd appearance		50%
	• 3rd appearance	Discontinue permanently	
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support		
	• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
	• 2nd appearance	Discontinue permanently	
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy			

Hand foot syndrome:

Table 5: Dose modification of capecitabine in hand foot syndrome

Toxicity Grade		Dose Modification
Grade 1	Skin changes (e.g., numbness, dysesthesia, paraesthesia, tingling, erythema) with discomfort not disrupting normal activities	100% Dose
Grade 2	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living	Withhold treatment until event resolves or decreases in intensity to grade 1.
Grade 3	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Withhold treatment until event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased

Treatment related hepatotoxicity

Table 6: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		ALT, AST	Dose Modification
> 3.0 x ULN	**or**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

mitoMYcin: Low (**Refer to local policy).**
Capecitabine: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: Not required

OTHER SUPPORTIVE CARE:

- Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy.
- Mouth Care **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.

mitoMYcin:

- **Extravasation:** mitoMYcin causes pain and tissue necrosis if extravasated **(Refer to local policy).**

Capecitabine:

- **Diarrhoea and dehydration:** This may be dose limiting. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated.
- **Cardiotoxicity:** Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of 5Fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.
- **Hand-foot syndrome (HFS**): HFS, also known as palmar-plantar erythrodysaesthesia (PPE), is a common side effect associated with capecitabine (see Table 5 for dose modification of capecitabine for HFS).

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing its toxicity. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

REFERENCES:

1. Glynne-Jones R, et al. Extra- A multicentre Phase II Study of Chemoradiation Using a 5 Day Per Week Oral Regimen of Capecitabine and Intravenous Mitomycin C in Anal Cancer. Int J Radiation Oncology Biol Phys 2008 Sep 1; 72 (1):119-26. Available at: https://pubmed.ncbi.nlm.nih.gov/18472366/
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. mitoMYcin 40mg powder and solvent for intravesical solution. Summary of Product Characteristics. Accessed Nov 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/387bf720-717c-4e6b-ae84-3a46d07161d9.pdf
5. Capecitabine (Xeloda®) Summary of Product Characteristics. Accessed Nov 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	08/09/2022		Prof Maccon Keane
2	08/02/2024	Reviewed. Updated renal and hepatic dose modifications table in line with recommendations by Giraud et al 2023.	Prof Maccon Keane
2a	14/05/2024	Amendment to reimbursement status column.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.