SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Cisplatin & Capecitabine (CisCAPanal)

Anal Cancer

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

Approved for use in:

Metastatic or Inoperable Locally Advanced Squamous Cell Anal Carcinoma

(2nd line when mitomycin is not available)

PS 0-2

Dosage:

Drug	Dosage	Route	Frequency
Cisplatin	60mg/m2	IV	Every 21 days
Capecitabine	1000mg/m^2 BD for 14 days, rest 7 days	PO	Every 21 days

Review after 4 cycles. Maximum 6 cycles if tolerated.

Administration & Counselling Points:

Capecitabine

- Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias or taking high dose aspirin or coumarin anticoagulants
- Teratogenic risk – advice on contraception
- 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

Cisplatin

- Review fluid intake over previous 24hours
- Ensure renal function is checked prior to commencing treatment
- Weigh patient before commencing IV hydration, before and after cisplatin infusion
- Monitor fluid balance. If fluid balance +1.5L, or weight gain of >1.5kg, consider furosemide 20-40mg
- Advised patient to stay hydrated (2L fluids over 24hrs) post-cisplatin

Emetogenic risk:

High – On Day 1
Low – During capecitabine therapy

Supportive treatments:

Aprepitant 125mg to be taken on day 1, an hour before chemotherapy and 80mg to be taken as a single dose on day 2 and day 3

Dexamethasone tablets, 4mg twice daily for 3 days

Metoclopramide 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:

Cisplatin – Irritant – apply warm compress to affected area for 20mins. Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

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

Creatinine Clearance (mL/min)	Cisplatin Dose	Capecitabine Dose
50 - 59	75%	Full dose
< 50	Not recommended (palliative intent) - Consider carboplatin + Capecitabine protocol	75%
< 30		Not recommended
<20	Carboplatin contraindicated	

Hepatic

Liver function	Cisplatin dose	Capecitabine dose
Bilirubin 1.5 to 3 x ULN AST/ALT 5 x ULN	No dose adjustment needed	100%
Bilirubin > 3 x ULN	No dose adjustment needed – cisplatin is not metabolised	No dose adjustment needed – monitor as associated with low capecitabine clearance

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

Interactions:

Capecitabine

- Folic acid – Avoid
- Clozapine – increased risk of agranulocyrosis
- Allopurinol – Avoid
- 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
Cisplatin
• Cephalosporins • Aminoglycosides • Amphotericin B • Contrast media • Avoid live vaccines • Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH – monitor INR • Antihistamines / Ifosfamide – may mask ototoxicity • Anticonvulsant (eg. Phenytoin) – may reduce anticonvulsant plasma levels - monitor

Treatment schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant (1hr pre-chemotherapy)	125mg	PO	
1	Ondansetron (30min pre-chemotherapy)	24mg	PO	
1	Dexamethasone (30min pre-chemotherapy)	12mg	PO	
1	Furosemide	20mg	PO	
1	Potassium Chloride 20mmol in Sodium Chloride 0.9%	1000ml	IV	Over 90minutes
1	Measure urine output volume and record If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes			

	If urine output still not adequate contact the medical team			
1	Cisplatin	60mg/m2	IV	In Sodium chloride 0.9% over 90 minutes
1	Potassium Chloride 20mmol in Sodium Chloride 0.9%	1000ml	IV	Over 90minutes
1 to 14	Capecitabine	1000mg/m^2 Twice daily (morning and evening)	PO	

Main toxicities:

Cisplatin
• Nephrotoxicity • Ototoxicity • Neuropathy
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

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing	Last cycle
Clinical Assessment	X		Pre cycle		Pre cycle	Alternate cycles or team discretion	
SACT Assessment	X	X	X	X	X	Every cycle	Check has OPD
FBC	X	X	X	X	X	Every cycle	X
U&E, calcium, & LFT	X	X	X	X	X	Every cycle	X
CrCl	X	X	X	X	X	Every cycle	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.	
CT scan (advanced CRC patients)	X					Inform consultant team if not booked	Check has date for CT
Informed Consent	X					Verbal each cycle	
Height	X						
Weight recorded	X	X	X	X	X	Every cycle	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.

Non- Haematological toxicity:

<table>
<tr><th colspan="2">Capecitabine</th></tr>
<tr><td>Diarrhoea</td><td>Loperamide, 4mg STAT, then 2mg after each loose stool with a maximum dose of 16mg/day, codeine may be added – see table below for dose reductions
<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>
</table></td></tr>
<tr><td>Stomatitis</td><td>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.
<table>
<tr><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
</table></td></tr>
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	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, 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.			

Capecitabine 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. BNF available via: https://bnf.nice.org.uk/
2. InterAACT trial - Clin Oncol. 2020 Aug 1;38(22):2510-2518. doi: 10.1200/JCO.19.03266.
3. Lancet - 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. Northern Cancer Alliance, Anti-emetic Guidelines for Chemotherapy Induced Nausea and Vomiting. North of England Cancer Network (northerncanceralliance.nhs.uk)
5. Cisplatin SPC - Cisplatin 1 mg/ml Sterile Concentrate - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
6. Capecitabine SPC - Capecitabine 500 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

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
January 2024	2.0	**Aaron Teoh, Advanced Cancer Pharmacist**	- New format - Updated indication - Added total duration, under Dosage - Added counselling points - Updated Supportive medications, addition of metoclopramide, and removal of domperidone

			- Updated Renal and Hepatic Impairment dose modifications - Added Interactions - Updated Non-Haematological toxicity as per CTACE grading, with management and dose reductions table - Added DPYD section with management