SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Capecitabine and Oxaliplatin 21 day cycle (CAPOX) Colorectal Cancer

PROTOCOL REF: MPHACAPOX
Version No. 4.0

Approved for use in:

- Adjuvant colorectal cancer stage 3 or high risk stage 2
- Advanced colorectal cancer (not in combination with cetuximab)
- Neoadjuvant treatment of colorectal cancer.

Dosage:

Adjuvant / Neoadjuvant

Drug	Dosage	Route	Frequency
Oxaliplatin	130 mg/m^2	IV	Every 21 days for 4 cycles
Capecitabine	1000 mg/m^2 BD for 14 days	PO	Every 21 days for 4 cycles

Advanced

Drug	Dosage	Route	Frequency
Oxaliplatin	130 mg/m^2	IV	Every 21 days
Capecitabine	1000 mg/m^2 BD for 14 days	PO	Every 21 days

Palliative patients will have re-assessment after 4 cycles; continue until designated course length complete, unacceptable toxicity or disease progression.

Administration & Counselling Points:

Caution in patients with pre-existing neurotoxicity

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

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.

Emetogenic risk (if applicable):

Moderate

Supportive treatments:

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

Dexamethasone tablets 4mg twice daily for 3 days

Ondansetron 8mg twice a day for 3 days

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

Extravasation risk (if applicable):

Oxaliplatin – Irritant

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)	**Oxaliplatin Dose**	**Capecitabine Dose**
Greater than 50	Give 100%	Give 100%
30 to 50	Max 85mg/m^2	Give 75%
Less than 30	Omit	Omit

If moderate impairment monitor closely and adjust oxaliplatin dose if deterioration or toxicity appears.

Hepatic

Liver function	**Oxaliplatin dose**	**Capecitabine dose**
Bilirubin less than 2.5 x ULN ALT/AST less than 2.5 x ULN	Can give 100% however defer cycle rather than give as single agent	Omit until recovery

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

Allopurinol – reduced efficacy of capecitabine – avoid

Clozapine – additive risk of agranulocytosis

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.

Treatment schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30 mins before chemotherapy	8mg	PO	
1	**Ondansetron** 30 mins before chemotherapy	16mg	PO	
1	**Oxaliplatin**	130mg/m^2	IV	500mL Glucose 5% infusion over 2 hours
Days 1 to 14	**Capecitabine**	1000mg/m^2 BD	PO	Twice daily, morning and evening for 14 days followed by 7 days off.

Adjuvant – every three weeks for 4 cycles

Advanced- every three weeks for 4 cycles, reassess and continue therapy subject to patient choice, tolerability and response

Neoadjuvant – every three weeks for 4 cycles

Main toxicities:

Oxaliplatin
Infusion reactions, neuro toxicity, myelosuppression, mucositis, diarrhoea, nausea and vomiting
Capecitabine
Myelosuppression, diarrhoea, Palmar Plantar Erythrodysesthesia (PPE or hand- foot syndrome), stomatitis, fatigue, asthenia, anorexia, cardiotoxicity (uncommon), ovarian failure/infertility, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism DPD deficiency – leads to severe early fluorouracil toxicity, affects approximately 3% of population, may be life threatening

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 normally only required if a patient has not had capecitabine or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. 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:

Complete this guidance in line with SPC/ other protocols or trial protocols

Haematological toxicity (if required):

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 75 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:

Oxaliplatin

<table>
<tr><td>Neurotoxicity – see notes below for specific cases</td><td>
<table>
<tr><th>Neurotoxicity</th><th>Oxaliplatin dose</th></tr>
<tr><td>Grade 1 any duration or grade 2 < 7days but resolving before next cycle</td><td>130mg/m^2</td></tr>
<tr><td>Grade 2 persisting for 7 days or Grade 3 resolved by next cycle</td><td>100mg/m^2</td></tr>
<tr><td>Grade 3 persisting to next cycle or any grade 4</td><td>Stop oxaliplatin</td></tr>
</table>
If oxaliplatin is discontinued, review the dose of capecitabine and consider increasing to 1250mg/m^2
</td></tr>
<tr><td>Acute cold related dysesthesia (CRD)</td><td>Transient paraesthesia of hands and feet as well as laryngopharyngeal dysesthesia (unpleasant sensations in throat) is</td></tr>
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	common. Onset is during or within hours of infusion and it resolves in minutes or days. Symptoms are exacerbated by cold – advise patients on suitable precautions e.g. avoid cold drinks. Should not require dose reduction, but if troublesome then infusion duration can be increased to 6 hours (see note below).
Laryngopharyngeal dysaesthesia	Stop infusion, provide symptomatic treatment. Resume at slower infusion rate. Give subsequent infusions over 6 hours (see note below).
Cumulative dose related sensory neuropathy	Usually occurs after a cumulative dose of 800mg/m^2. Peripheral neuropathy can be a **permanent significant side effect** that can occur during or after treatment is completed. Patients should be informed of this risk. **If this symptom worsens or becomes permanent senior review should be requested.**
Allergic reactions during infusion	Stop the infusion and call for help. Follow trust anaphylaxis policy. Treat with IV corticosteroid and antihistamine. There is no need to stop the capecitabine. Discuss re-challenge with consultant

Whilst the recommended increase in duration of infusion is to 6 hours – where the oncologist and the treating team agree, this can be reduced to 4 hours dependent on the severity of the reaction and the tolerability of the infusion over this time.

Capecitabine

Toxicity	Management
Diarrhoea	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.				
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, refer to consultant, if symptoms persist stop capecitabine permanently.				

Capecitabine dose adjustments guidelines according to Common Toxicity Criteria

For diarrhoea, vomiting, mucositis, and PPE.

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		80%
-3rd appearance		60%
-4th appearance	Discontinue treatment permanently	Not applicable
• Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	80%
-2nd appearance		60%
-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	60%
-2nd appearance	Discontinue permanently	Not applicable

References:

1. Oxaliplatin summary of product characteristics accessed 19/02/2023 https://www.medicines.org.uk/emc/product/3024
2. Capecitabine summary of product characteristics accessed 19/02/2023 https://www.medicines.org.uk/emc/product/14590/smpc
3. BNF available via: https://bnf.nice.org.uk/
4. NICE: CG151 Colorectal cancer: diagnosis and management. Published: 29 January 2020 Last updated: 15 December 2021

Circulation/Dissemination

Date added into Q-Pulse	20th April 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
Feb 2022	4.0	**Joanne McCaughey, Deputy Chief Pharmacist**	New format, change to criteria.