Systemic Anti Cancer Treatment Protocol

Oxaliplatin & Capecitabine (Ox-Cap)

PROTOCOL REF: MPHAOXCAP
(Version No: 1.1)

Approved for use in:

Neoadjuvant treatment of colorectal cancer

Advanced colorectal RAS wild type first line (if not for cetuximab)

Advanced colorectal RAS mutated first line

Advanced colorectal RAS wild type after progression with first line irinotecan

Advanced colorectal RAS Mutated after progression with first line irinotecan

Operable or inoperable rectal cancer

See XELOX protocol for adjuvant use

Dosage:

Drug	Dosage	Route	Frequency
Oxaliplatin	85mg/m^2	IV	Every 14 days
Capecitabine	900mg/m^2 BD for 9 days	PO	Every 14 days

Reassess after 6 cycles and continue subject to patient choice, tolerability and response

Supportive treatments:

Antiemetic Risk – Moderate – follow antiemetic policy

Dexamethasone tablets 4mg twice daily for 3 days

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

Loperamide 4mg immediately after first liquid stool followed by 2mg every 2 hours for at least 12 hours

Extravasation risk:

Oxaliplatin – Irritant, Follow trust / network extravasation policy.

Administration:

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**	85mg/m^2	IV	In 500mL glucose 5% over 2 hours
Days 1 to 9	**Capecitabine**	900mg/m^2 BD	PO	Take twice daily, morning and evening for 9 days followed by 5 days off

or 6 cycles and reassess, continue subject to patient choice, tolerability and response

Notes:

Be aware of possible infusion related reactions with oxaliplatin and administer pre-meds as prescribed

Caution in patients with pre-existing neurotoxicity – see below

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

Correct any magnesium deficiency before giving oxaliplatin

Be aware of infusion related allergic reactions – see below

Do not start capecitabine if baseline ANC<1.0 x 10^9/L OR platelets < 100 x 10^9/L

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:

Capecitabine

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

Main Toxicities:

Oxaliplatin

Infusion reactions, neuro toxicity, myelosuppression, mucocitis, diarrhoea, nausea and vomiting

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 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
Medical Assessment	X		X		X	Alternate cycles
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	Every cycle
CrCl	X	X	X	X	X	Every cycle
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. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
CT scan	X					
Informed Consent	X					
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if all apply:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

Delay 1 week on day 1 if any apply:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 74 x 10^9/L

If platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction as follows

Lowest count since previous cycle	**Oxaliplatin dose**	
Grade 3 / 4 neutropenia (<1.0 x10^9/L) or thrombocytopenia (<50 x 10^9/L)	65mg/m^2 (metastatic) 75mg/m^2 (adjuvant)	

Non-haematological toxicity

Renal

Calculate CrCl using Cockroft and Gault before each cycle. If renal function falls by >30% than expected value consider EDTA clearance

Creatinine Clearance (mL/min)	**Oxaliplatin Dose**	**Capecitabine Dose**
>50	Full dose	Give 100%
30 to 50	Full dose	Give 75%
<30	Omit	Omit

Hepatic

Liver function	**Oxaliplatin dose**	**Capecitabine Dose**
Bilirubin > 3 x ULN	100%	Omit

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**

<table>
<tr><th colspan="2">Oxaliplatin</th></tr>
<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>85mg/m^2</td></tr>
<tr><td>Grade 2 persisting for 7 days or Grade 3 resolved by next cycle</td><td>65mg/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 infusional dose of fluorouracil and consider increasing to 2800mg/m^2
</td></tr>
<tr><td>Acute cold related dysaesthesia (CRD)</td><td>Transient paraesthesia of hands and feet as well as laryngopharyngeal dysaesthesia (unpleasant sensations in throat) is 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)</td></tr>
<tr><td>Laryngopharyngeal dysaesthesia</td><td>Stop infusion, provide symptomatic treatment. Resume at slower infusion rate. Give subsequent infusions over 6 hours</td></tr>
<tr><td>Cumulative dose related sensory neuropathy</td><td>Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment is completed, is usually reversible taking about 3-5 months to recover</td></tr>
<tr><td>Allergic reactions during infusion</td><td>Stop the infusion and call for help. Follow trust anaphylaxis policy. Treat with IV corticosteroid and antihistamine. Discuss continuing with fluorouracil alone or re-challenge with the consultant.</td></tr>
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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

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

Capecitabine Dose adjustment guidelines according to CTC

Including diarrhea, vomiting, stomatitis, and PPE

Common Toxicity Criteria	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% (consultant approval only)
-2nd appearance	Discontinue permanently	Not applicable

References:

CCC Policy - Prevention and Management of Extravasation Injuries Policy
https://extranet.clatterbridgecc.nhs.uk/index.php/intranet/policies-and-corporate-documents/policies/clinical

Summary of product characteristics, Electronic medicines compendium, SPC Xeloda©, https://www.medicines.org.uk/emc/medicine/4619 and Oxaliplatin, https://www.medicines.org.uk/emc

Xelox 1 Metastatic study (Roche), Protocol No 16966, 2004
Cassidy,J et al; JCO 2004; 22 (11); 2084 2091