OXALIPLATIN AND CAPECITABINE

1. First-line or subsequent use for metastatic colorectal cancer
2. Funding agreed for adjuvant use in high risk Stage II and Stage III colon and rectal cancer

Drugs/Dosage:	Oxaliplatin	130mg/m^2	IV	Day 1
	Capecitabine	1000mg/m^2	PO	twice daily from the evening of Day 1 to the morning of Day 15, followed by 7 days rest

Administration: Oxaliplatin in 500ml glucose 5% over 2 hours
Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

Frequency: Advanced: 3 weekly cycle for 4 cycles, then CT scan and clinical review
Adjuvant: 3 weekly cycle for 8 cycles

Main Toxicities: myelosuppression; mucositis; diarrhoea; neurotoxicity (see Comments); hand-foot syndrome (PPE); allergic reactions (see Comments); cardiotoxicity (uncommon); ovarian failure/infertility

Anti- emetics: D1 - highly emetogenic; D2 – D14 – mildly emetogenic

Regular Investigations:	FBC	Day 1
	U&Es & LFTs	Day 1
	Mg^{2+}	Day 1 (ideally, correct any low Mg^{2+} before oxaliplatin given)
	CEA	every 6 weeks
	ECG	if previous history of heart disease
	CT scan	after 4 cycles, in metastatic setting only

Comments: **Oxaliplatin and Neurotoxicity**

Acute - cold-related dysaesthesia (CRD):
Many patients experience transient paraesthesia of hands & feet, and some experience laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion, and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patient should be well advised on precautions to be taken. Does not require treatment or dose reduction.
For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium + 1gram of calcium gluconate in 250ml 0.9% sodium chloride over 1 hour, prior to starting the oxaliplatin, should also be made. NB. This management may also benefit patients who complain of pain/weakness in arm during oxaliplatin administration, but should **not** be used to try and alleviate CRD or cumulative neuropathy.

Cumulative - dose related peripheral sensory neuropathy:
Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

Allergic reactions to oxaliplatin during infusion: Immediate intervention is to stop the infusion and call for medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU.
At Consultant discretion, the patient may be re-challenged with oxaliplatin, according to the grade of reaction, as detailed in the separate document "Oxaliplatin Hypersensitivity & desensitisation regimen".

Reason for Update: allergic reactions updated; Mg & Ca use reviewed	Approved by Consultant: Dr S Essapen
Version: 5	Approved by Lead Chemotherapy Nurse: V Mumford
Supersedes: Version 4	Date: 30.12.13
Prepared by: S Taylor	Checked by: C Tucker

Dose Modifications

Haematological Toxicity on D1:	Neutrophils ≥ 1.5 x 10^9/l and Platelets ≥ 75 x 10^9/l	Proceed with treatment, if necessary adjusting doses for any previous haematological toxicity as specified below:
	Neutrophils 1.0 – 1.4 x 10^9/l or Platelets 50 - 74 x 10^9/l	Delay treatment for 1 week. Repeat FBC and, if recovered, no dose adjustment required. This applies whether this is 1st, 2nd or 3rd occurrence.
	Neutrophils 0.5 – 0.9 x 10^9/l or Platelets 10 - 49 x 10^9/l	Delay treatment for 1 week. Repeat FBC and, if recovered, give 75% of original capecitabine dose and oxaliplatin 100mg/m^2. If 2nd occurrence, maintain capecitabine dose but reduce oxaliplatin to 85mg/m^2.
	Neutrophils < 0.5 x 10^9/l or Platelets < 10 x 10^9/l	Delay treatment for 1 week. Repeat FBC and, if recovered, give 50% of original capecitabine dose and oxaliplatin 85mg/m^2. If any reoccurrence of Grade 4 haematological toxicity, discontinue treatment.

If patient suffers an episode of Grade 3 febrile neutropenia, continue after recovery with oxaliplatin 85mg/m^2 and capecitabine at 75% of original dose. For Grade 4 neutropenic sepsis or 2nd occurrence of grade 3, discuss with Consultant.

Renal Impairment: Before every cycle, calculate CrCl using Cockcroft and Gault. If borderline, an EDTA should be requested.

Creatinine Clearance (ml/min)	Capecitabine Dose	Oxaliplatin Dose
> 50	Give 100% dose	Give 100% dose
30 – 50	Give 75% dose	Give 100% dose
< 30	Omit	Omit

Hepatic Impairment: If bilirubin > 3 x ULN or ALT/AST > 2.5 ULN, omit capecitabine until liver function recovers.

Non-Haematological Toxicities: **Note that severe diarrhoea and/or severe mucositis early in capecitabine treatment can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.**

Toxicity due to capecitabine administration may be managed symptomatically and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

Capecitabine Dose Adjustment Guidelines according to CTC

These dosing guidelines are for side effects including diarrhoea, vomiting, mucositis and PPE.

Common Toxicity Criteria	During Course of Therapy	Dose adjustment for next cycle (% of start dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2: 1st appearance	Interrupt until resolved to Grade 0–1*	Give 100% dose
Grade 2: 2nd appearance	Interrupt until resolved to Grade 0–1*	Give 75% dose
Grade 2: 3rd appearance	Interrupt until resolved to Grade 0–1*	Give 50% dose
Grade 2: 4th appearance	Discontinue treatment permanently	
Grade 3: 1st appearance	Interrupt until resolved to Grade 0–1*	Give 75% dose
Grade 3: 2nd appearance	Interrupt until resolved to Grade 0–1*	Give 50% dose
Grade 3: 3rd appearance	Discontinue treatment permanently	
Grade 4: 1st appearance	Discontinue permanently **or,** only with Consultant approval, interrupt until resolved to Grade 0-1	Give 50% dose (Consultant approval only)

***** For Grade ≥ 2 **diarrhoea**, capecitabine should not be restarted until resolved to Grade 0-1 **and** no loperamide has been given for 24 hours (or back to "baseline" loperamide doses, in adjuvant patients with an ileostomy)

Neurological Toxicity:

Grade 1 of any duration or grade 2 paraesthesias lasting longer than 7 days but resolved before the next cycle is due, continue with oxaliplatin 130mg/m^2.
Grade 2 paraesthesias persisting until next cycle; reduce oxaliplatin dose to 100mg/m^2.
Grade 3 paraesthesias lasting longer than 7 days but resolved before next cycle is due; reduce oxaliplatin dose to 100mg/m^2.
Grade 3 paraesthesias persisting until next cycle or Grade 4 of any duration, discontinue oxaliplatin permanently.

Cardiotoxicity:

Exercise caution in patients with prior history of coronary heart disease, arrhythmias or angina.

References:

Cassidy, J et al; JCO 2004; 22 (11); 2084 – 2091
Xelox 1 Metastatic Study (Roche), Protocol No NO16966, 2004
Schmoll, H-J et al; JCO 2007; 25: 102 – 109 (Xeloxa adjuvant study)
Haller, D et al; Eur J Cancer Supp 2009; 7(3): 4