XELOX - Capecitabine and Oxaliplatin (colorectal)

Indication

Adjuvant treatment of stage III colon cancer.

Advanced metastatic colorectal cancer.

(NICE CG131)

ICD-10 codes

Codes prefixed with C18-20.

Regimen details

Day	Drug	Dose	Route
1	Oxaliplatin	130mg/m^2	IV infusion
1-14	Capecitabine	1000mg/m^2 BD	PO

Cycle frequency

21 days

Number of cycles

Maximum 8 cycles.

Administration

Oxaliplatin is administered in 250mL glucose 5% over 2 hours.
Oxaliplatin is not compatible with sodium chloride 0.9%. Lines must not be piggybacked or flushed with sodium chloride 0.9% immediately after the infusion.

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Chlorphenamine 10mg IV may be administered.
Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of oxaliplatin and appropriate therapy should be initiated.

Oxaliplatin may cause transient paraesthesia of hands and feet and 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 patients should be well advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Capecitabine is available as 150mg and 500mg tablets.
Tablets should be taken after food and swallowed whole with a glass of water.

Doses should be prescribed as per the following table:

Body surface area (m^2)	Dose level 1000mg/m^2 BD
	Dose to be prescribed (mg)
1.24-1.38	1300mg BD
1.39-1.47	1450mg BD
1.48-1.57	1500mg BD
1.58-1.72	1650mg BD
1.73-1.89	1800mg BD
1.90-2.07	2000mg BD
2.08-2.22	2150mg BD
≥2.23	2300mg BD

Pre-medication

Antiemetics as per local policy.

Patients who have previously experienced Grade 1 or 2 platinum hypersensitivity should receive the following premedication:

- 45 minutes prior to oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to oxaliplatin: Chlorphenamine 10mg IV and Ranitidine 50 mg IV

Patients who develop peripheral neuropathy may be considered for calcium gluconate 1g and magnesium sulphate 1g given together in 250mL 5% glucose IV over 20 minutes pre- and post-oxaliplatin infusion. Caution is required in giving this treatment to patients with known hypercalcemia or those receiving therapy with digoxin or thiazide diuretics.

Emetogenicity

This regimen has a moderate-high emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.

Loperamide if required.

Extravasation

Oxaliplatin is an exfoliant (Group 4).

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	< 1.5 x ULN
AST/ALT	< 3 x ULN
Creatinine Clearance (CrCl)	≥ 50mL/min

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and platelets < 75 x 10^9/L stop capecitabine and delay next cycle until recovery. The recommence with dose modifications as below:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Oxaliplatin dose**	**Capecitabine dose**
≥ 1.0	and	≥ 75	100%	100%
0.5-0.9	or	50-74	100mg/m^2	100%
< 0.5	and/or	25-49	100mg/m^2	100%
< 0.5	and/or	< 25	65mg/m^2	100%

If febrile neutropenia (neutrophils < 0.5 x 10^9/L and fever requiring IV antibiotics) – reduce all subsequent doses of oxaliplatin to 100mg/m^2.

- **Renal impairment**

CrCl (mL/min)	**Oxaliplatin dose**	**Capecitabine dose**
≥ 50	100%	100%
30-49	75%	75%
< 30	Omit	Contraindicated

- **Hepatic impairment**

Capecitabine:

Lack of information available. In patients with mild to moderate hepatic dysfunction due to liver metastases (bilirubin < 3 x ULN and/or AST/ALT < 5 x ULN). Probably no dose reduction necessary, consultant decision.

Oxaliplatin:

Little information available. Probably no dose reduction necessary, consultant decision.

- **Other toxicities**

Capecitabine:

Other toxicities should be managed by symptomatic treatment and/or dose modification (i.e. by treatment interruption or undertaking a dose reduction).

Once the dose has been reduced, it should not be increased at a later time.

Dose modifications should be made as per the following table:

Toxicity grade	**1st occurrence**	**2nd occurrence**	**3rd occurrence**	**4th occurrence**
0-1	100%	100%	100%	100%
2	Delay then 100%	Delay then 75%	Delay then 50%	Discontinue
3	Delay then 75%	Delay then 50%	Discontinue	
4	Delay then 50%	Discontinue		

Any delays should be until the toxicity has resolved to grade 0-1.

Oxaliplatin:
Neurological toxicity:
If neurological symptoms occur, use the following oxaliplatin dose adjustments:

Toxicity grade	Oxaliplatin dose
1	100%
2 (persisting until next cycle)	100mg/m^2
3 (>7 days but resolved before next cycle)	100mg/m^2
3 (persisting until next cycle) or 4	Discontinue

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Allergic reactions
Neurotoxicity
Nephrotoxicity
Coronary artery spasm*

*Coronary artery spasm is a recognised complication of fluorouracil treatment, although the evidence base regarding aetiology, management and prognosis is not particularly strong.
Coronary artery spasm is more common in patients receiving continuous infusions of fluorouracil, and is usually reversible on discontinuing the infusion. Should a patient receiving fluorouracil present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the fluorouracil should be permanently discontinued.

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema
Alopecia
Fatigue
Dyspnoea

- **Other side effects**

Headache
Dizziness
Dysgeusia

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Oxaliplatin:
Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin.

Capecitabine:
Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of capecitabine.
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Phenytoin and fosphenytoin – toxicity has occurred during concomitant capecitabine therapy – monitor levels regularly.

Sorivudine and its analogues – co-administration causes increased toxicity which may be fatal.
Allopurinol – A decrease in capecitabine activity as been shown when taken in combination of allopurinol. Avoid if possible.
Antacids – the use of antacids with capecitabine can decrease absorption – avoid.

Additional comments

This regimen is contraindicated if known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency

Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

References

- National Institute for Health and Clinical Excellence. Clinical Guidance 131 accessed £ Sept 2014 via www.nice.org.uk
- Summary of Product Characteristics Oxaliplatin (Sanofi) accessed 3 Sept 2014 via www.medicines.org.uk
- Summary of Product Characteristics Capecitabine (Roche) 3 Sept 2014 via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.

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