EOX - Epirubicin, Oxaliplatin and Capecitabine (oesophagus)

Indication
First line palliative treatment for locally advanced, inoperable oesophago-gastric cancer for patients unsuitable for radical therapy.

ICD-10 codes
Codes prefixed with C15

Regimen details

Day	Drug	Dose	Route
1	Epirubicin	50mg/m^2	IV bolus
1	Oxaliplatin	130mg/m^2	IV infusion
1-21	Capecitabine	625mg/m^2 BD	PO

Cycle frequency
21 days

Number of cycles
Maximum of 8 cycles.

Administration
Epirubicin is administered first by slow intravenous bolus in to the side arm of a fast flowing drip of sodium chloride 0.9%.

Oxaliplatin is administered in 250-500mL glucose 5% over 2 hours. If patients experience laryngo-pharyngeal dyaesthesia (see below), subsequent infusions should be should be given over 4-6 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.

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 625mg/m^2 BD
	Dose to be prescribed (mg)
1.25-1.36	800mg BD
1.37-1.52	1000mg morning and 800mg evening
1.53-1.66	1000mg BD
1.67-1.78	1150mg morning and 1000mg evening
1.79-1.90	1150mg BD
1.91-2.04	1300mg morning and 1150mg evening
2.05-2.16	1300mg BD
2.17-2.32	1500mg morning and 1300mg evening
≥2.33	1500mg BD

Pre-medication

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 high emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Loperamide if required.

Extravasation

Epirubicin is a vesicant (Group 5)
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
Magnesium	14 days
Calcium	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
Magnesium	7 days
Calcium	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
Creatinine Clearance (CrCl)	> 50mL/min

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose**
≥ 1.0	and	≥ 75	100%
0.5 - < 1.0	or	50-74	Stop Capecitabine Delay until count recovery Restart: Epirubicin 75% dose, Oxaliplatin 100mg/m^2, Capecitabine 100% dose

- **Renal impairment**

CrCl (mL/min)	**Epirubicin dose**	**Oxaliplatin dose**	**Capecitabine dose**
> 50	100%	100%	100%
30-49	100%	75%	75%
< 30	omit	omit	contraindicated

- **Hepatic impairment**

Bilirubin (x ULN)	**Epirubicin dose**
< 1.5	100%
1.5-3	50%
3-5	25%
> 5	omit

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
Cardiomyopathy
Nephrotoxicity
Severe toxicity due to DPD deficiency (see comments below)

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema
Alopecia
Fatigue
Pink urine (for 24 hours post epirubicin)

- **Other side effects**

Dysguesia
Headache
Dizziness

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.

Epirubicin has a life time maximum cumulative dose of 900mg/m2

References

- Summary of Product Characteristics Oxaliplatin (Sanofi) accessed 18 June 2014 via www.medicines.org.uk
- Summary of Product Characteristics Capecitabine (Roche) accessed 18 June 2014 via www.medicines.org.uk
- Summary of Product Characteristics Epirubicin (Sanofi) accessed 18 June 2014 via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.
- Cunningham D, Rao S, Starling N, Iveson T, Nicolson M, Coxon F, et al. Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophago-gastric (OG) cancer: The REAL 2 trial. J Clin Oncol 2006. 24;18S (June 20 supplement abstract):4017

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