ECX - Epirubicin, Cisplatin and Capecitabine (upper GI)

Indication

Palliative therapy for stage IV or relapsed oesophageal or gastric cancer.

Induction therapy prior to surgery or definitive irradiation.

ICD-10 codes

Codes prefixed with C15 or C16

Regimen details

Day	Drug	Dose	Route
1	Epirubicin	50mg/m^2	IV bolus
1	Cisplatin	60mg/m^2	IV infusion
1-21	Capecitabine	625mg/m^2 BD	PO

Cycle frequency

21 days

Number of cycles

Maximum of 8 cycles (4 cycles for induction therapy).

Administration

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

Cisplatin is administered in 500mL sodium chloride 0.9% over 60 minutes following the pre and post hydration protocol below.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	1 hour
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	30 minutes 30 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. Give a single dose of furosemide 20mg iv if necessary.		
Cisplatin	500mL	1 hour
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700mL or 2900mL**	**4 hours 30 minutes**

Note: Patients with low magnesium or low potassium should have 2g $MgSO_4$ and 20mmol KCl added to the pre-hydration bag and the duration of the infusion increased to 2 hours.

All patients must be advised to drink at least 2 litres of fluid over the following 24 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
Hydration regimen as above.

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)
Cisplatin 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)	> 60mL/min

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Action**	**Capecitabine dose**	**Epirubicin dose**	**Cisplatin dose**
≥ 1.0	and	≥ 75	Go ahead	100%	100%	100%
0.5-0.9	and/or	50-74	Stop capecitabine Delay next cycle until count recovery	100%	75%	100%
< 0.5	and/or	25-49	Stop capecitabine Delay next cycle until count recovery	100%	50%	100%
< 0.5	and/or	< 25	Stop capecitabine Delay next cycle until count recovery	100%	omit	100%

In the case of febrile neutropenia during the previous cycle, treat as follows:

- Grade 3 febrile neutropenia (neutrophil count <1.0x10^9/L), restart capecitabine and cisplatin at 100% dose and epirubicin at 50% dose.
- Grade 4 febrile neutropenia (neutrophil count <0.5x10^9/L), restart capecitabine and cisplatin at 50% dose and stop epirubicin.

- **Renal impairment**

CrCl (mL/min)	**Epirubicin dose**	**Cisplatin dose**	**Capecitabine dose**
> 60	100%	100%	100%
50-60	100%	75%	100%
45-49	100%	50% or carboplatin AUC 5	75%
30-44	100%	carboplatin AUC 5	75%
20-29	100%	carboplatin AUC 5	omit
< 20	Discontinue	Discontinue	Discontinue

- **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.

Cisplatin:
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. Capecitabine should be omitted and treatment delayed until the toxicity has resolved to grade 0-1. Once the dose has been reduced, it should not be increased at a later time.

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.

Cisplatin:
Neurotoxicity or ototoxicity:

- ≥ Grade 2: permanently stop cisplatin and switch to carboplatin AUC 5.

Diarrhoea: reduce doses as follows:

- Grade 2: 75% dose
- Grade 3: 50% dose
- Grade 4: discontinue or 50% dose (consultant decision)

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

- **Serious side effects**

Myelosuppression
Infertility
Cardiomyopathy
Nephrotoxicity
Secondary malignancy
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.

Allopurinol and antigout agents: interactions have been observed between allopurinol and fluorouracil with possible decreased efficacy of fluorouracil. Concomitant use of allopurinol with capecitabine should be avoided. Cisplatin may increase the concentration of blood uric acid. Thus, in patients concurrently receiving **antigout**

agents such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricemia and gout.

Cisplatin:
Avoid ototoxic and nephrotoxic agents (including aminoglycosides, loop diuretics and amphotericin B) as these may increase toxicity of cisplatin.

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.

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.

Epirubicin has a life time maximum cumulative dose of 900mg/m^2

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed 25 June 2014 via www.medicines.org.uk
- Summary of Product Characteristics Capecitabine (Roche) accessed 25 June 2014 via www.medicines.org.uk
- Summary of Product Characteristics Epirubicin (Sanofi) accessed 25 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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