ECX - Epirubicin, Cisplatin and Capecitabine (upper GI)

Indication
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 into 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 pre and post hydration

Pre and post hydration consists of 20mmol potassium chloride and 10mmol magnesium sulfate given in 1 litre 0.9% sodium chloride over 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.

For patients with swallowing difficulties, capecitabine can be added to approx. 200ml warm water and stirred until completely dissolved. The solution can be drunk or administered via a feeding tube

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

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy.

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	48 hours
U+E (including creatinine)	48 hours
LFTs	48 hours
Magnesium	48 hours
Calcium	48 hours

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

- http://www.swscn.org.uk/guidance-protocols/cancer-protocols/ accessed 9 Jul 2020
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- 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

THIS PROTOCOL HAS BEEN DIRECTED BY DR MITCHELL, DESIGNATED LEAD CLINICIAN FOR UPPER GI CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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