EPIRUBICIN CISPLATIN CAPECITABINE (ECX)

INDICATION (ICD10) D37

1. Unknown primary adenocarcinoma if appropriate (unlicensed)
PS 0, 1, 2

REGIMEN

Day 1	Prehydration	
	EPIRUBICIN	50mg/m^2 IV bolus
	CISPLATIN	60mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
	Posthydration	
Days 1 to 21	CAPECITABINE 625mg/m^2 twice daily (1250mg/m^2/day) oral continuously	

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days
Advanced - up to 6 cycles

ADMINISTRATION

Tablets should be taken 12 hours apart.
Swallowed with water within 30 minutes after a meal, or dissolve in 200ml luke warm water, stir thoroughly (squash may be added if unpalatable).

ANTI-EMETICS

Highly emetogenic day 1
Low emetogenic risk days 2 to 21

CONCURRENT MEDICATION REQUIRED

Capecitabine	Mouth and bowel support eg Loperamide, benzydamine mouthwash
Cisplatin	Ensure adequate pre and post hydration. If urine output is <100ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40mg furosemide PO/IV.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cisplatin – exfoliant
Epirubicin - vesicant

Central or peripheral

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Ideally EDTA GFR should be used. Creatinine clearance calculated, at the Consultant's discretion.
Serum creatinine
ECG (possible ECHO) required if patient has preexisting cardiac disease
Baseline weight and every cycle
DPYD (dihydropyrimidine dehydrogenase) test

MAIN TOXICITES AND ADVERSE REACTIONS

Capecitabine	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine Cardiotoxicity – monitor cardiac function (consider ECG at baseline). To minimise risk of anthracycline induced cardiac failure signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue. All patients should be told to report any cardiac symptoms immediately and should be told to stop the medication immediately if any suspicion of cardiac problems. Stomatitis
Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Epirubicin	Cardiotoxicity – monitor cardiac function (consider ECG at baseline). Epirubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Capecitabine	Brivudine and analogues should be avoided Warfarin Phenytoin Allopurinol
Cisplatin	Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Cisplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

DOSE MODIFICATIONS

Epirubicin maximum lifetime dose
= 650mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
= 1000mg/m^2 (with normal cardiac function)

DPYD variant identified follow national or local DPD dose modification guidelines.

Haematological

Platelets ≥100x10^9/L neutrophils ≥1.5x10^9/L	Give 100% dose
Platelets 50-100x10^9/L neutrophils 0.5-1.5x10^9/L	Stop capecitabine, delay cisplatin and epirubicin until recovery. Restart capecitabine and cisplatin at 100% dose give 75% epirubicin dose on subsequent cycles
Platelets 25-49x10^9/L neutrophils <0.5x10^9/L	Stop capecitabine, delay cisplatin and epirubicin until recovery. Restart capecitabine and cisplatin at 100% dose, give 50% epirubicin dose on subsequent cycles
Platelets <25x10^9/L	Stop capecitabine, delay cisplatin and epirubicin until recovery. Restart capecitabine and cisplatin at 100% dose BUT omit epirubicin from subsequent cycles

Non-haematological

Capecitabine

Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and handfoot syndrome.

Toxicity can be managed by symptomatic treatment 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.

When capecitabine is stopped for toxicity, the doses are omitted and not delayed.

Toxicity grades	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 2 - 1st appearance	Interrupt until resolved to grade 0-1	100%
Grade 2 - 2nd appearance	Interrupt until resolved to grade 0-1	75%
Grade 2 - 3rd appearance	Interrupt until resolved to grade 0-1	50%
Grade 2 - 4th appearance	Discontinue treatment permanently	Not applicable
Grade 3 - 1st appearance	Interrupt until resolved to grade 0-1	75%
Grade 3 - 2nd appearance	Interrupt until resolved to grade 0-1	50%
Grade 3 - 3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 - 1st appearance	Discontinue permanently OR if physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
Grade 4 - 2nd appearance	Discontinue treatment permanently	Not applicable

Cisplatin

If patient complains of tinnitus, tingling of fingers and/or toes, discuss with SpR or Consultant before administration.

Hepatic impairment

Capecitabine

Bilirubin of >3xULN or ALT/AST >2.5xULN	Interrupt capecitabine Treatment may be resumed when bilirubin decreases to <3xULN or hepatic aminotransferases decrease to <2.5xULN.

Cisplatin

No need for dose adjustment

Epirubicin

Bilirubin 24-50micromol/L	give 50% dose
Bilirubin 51-85micromol/L	give 25% dose
Bilirubin >85micromol/L	omit

Renal impairment

Capecitabine

CrCl (ml/min) >50	give 100% dose
CrCl (ml/min) 30 -50	give 75% dose
CrCl (ml/min) <30	contraindicated

Cisplatin

GFR >60ml/min	give 100% dose
GFR 50-59ml/min	give 75% dose
CrCl 40-49ml/min	give 50% dose (curative intent) not recommended (palliative intent)
GFR <40ml/min	Not recommended, consider carboplatin AUC 4 or 5 every 4 weeks or switch to an appropriate oxaliplatin containing regimen

Epirubicin

Serum creatinine >442micromol/L	May require dose adjustment

REFERENCES

1. REAL 2 trial (arm 3)
2. ST03 trial