E – CARBO – X

For use in patients who are not eligible for entry into clinical trial, nor suitable for cisplatin administration
For locally advanced (inoperable) or metastatic oesophageal or gastric cancer;
peri-operative use in oesophageal or gastric cancer;
adenocarcinoma of unknown primary

Drug/Dosage:	Epirubicin	50mg/m^2	IV Day 1
	Carboplatin	AUC 5 (AUC3 if concerned – see Comments)	IV Day 1
	Capecitabine	625mg/m^2 PO BD daily throughout treatment	

Administration: Capecitabine tablets (available as 500mg and 150mg) should be swallowed whole with water within 30 minutes after a meal.
Information, provided by Roche, is available via Pharmacy regarding dispersing the ablets for those patients with swallowing difficulties or with feeding tubes.
Epirubicin administered via fast running infusion of 0.9% Sodium Chloride
Carboplatin in 250ml of Glucose 5% over 30 minutes

Frequency: 3 weekly cycle
Advanced / metastatic use: up to 6 cycles
All patients for full clinical review after 3 cycles - for locally advanced cases with no other assessable disease, a restaging OGD to assess mucosal response is required after Cycle 3.
Perioperative use: 3 cycles before surgery, plus a further 3 cycles post surgery

Main toxicities: myelosuppression; thrombocytopenia; alopecia; mucositis; diarrhoea; plantar/palmar syndrome (PPE); cardiomyopathy; cardiotoxicity due to capecitabine (see Comments); ovarian failure/infertility

Anti-emetics: Day 1: highly emetogenic Days 2 – 22: mildly emetogenic

Extravasation: Epirubicin is a vesicant

Regular Investigations:	FBC	D1
	LFTs	D1
	U&Es	D1
	EDTA	Prior to 1st cycle
	MUGA scan	see Comments
	Restaging	after Cycle 3 (see Frequency)

Comments: Maximum cumulative dose Epirubicin = 950mg/m^2
A baseline MUGA scan should be performed where the patient is considered at risk of having significantly impaired cardiac contractility. If ejection fraction is less than 50%, an alternative regimen should be given. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

Carboplatin dose should be calculated using the Calvert formula:
Dose = Target AUC x (25+GFR)
If EDTA not yet available, Cockcroft and Gault may be used to predict GFR on Cycle 1, but dose must be corrected according to measured EDTA for the remaining cycles.
EDTA should only be repeated if there is a 30% change in serum creatinine.

Reason for Update: Restaging requirements added / max no of cycles = 6	Approved by Lead Chemotherapy Nurse: C Palles-Clark
Version: 2	Approved by Consultant: Dr G Middleton
Supersedes: Version 1	Date: 1.4.08
Prepared by: S Taylor	Checked by: S Seymour

For patients with performance status 2 or who are considered at increased risk of neutropenia, consider giving carboplatin AUC 3 with dose escalation to AUC 5 if well tolerated.

Fluoropyrimidine therapy has been associated with cardiotoxicity (including myocardial infarction, angina, arrhythmias, cardiogenic shock, sudden death and ECG changes). Therefore, exercise caution in patients with prior history of coronary heart disease, arrhythmias and angina pectoris.

Dose Modifications

Haematological Toxicity:

WBC < 3.0 x 10^9/l
or
Neutrophils < 1.5 x 10^9/l
or
Platelets < 100 x 10^9/l

Stop capecitabine, and delay epirubicin and carboplatin for one week.
Repeat FBC after one week and, if normal, resume treatment at full dose.

If there is a 2 week delay, give epirubicin and carboplatin at 75% dose.
If there is a > 2 week delay, give epirubicin and carboplatin at 50% dose.

If patient suffers an episode of Grade 3 febrile neutropenia at any time, continue after recovery with 25% dose reduction for epirubicin and carboplatin AUC 4. For any Grade 4 neutropenic sepsis, discuss with Consultant before proceeding with 50% dose reduction for epirubicin and carboplatin.

Renal Impairment: If EDTA or calculated CrCl < 20ml / min, carboplatin is contra-indicated.

CrCl (ml/min)	Capecitabine Dose
> 50	Give 100% dose
30 – 50	Give 75% dose
< 30	Omit

Hepatic Impairment:

Bilirubin (µmol/l)	Epirubicin Dose
24 – 51	Give 50% dose
52 – 85	Give 25% dose
> 85	Omit

If bilirubin > 3 x ULN or ALT/AST > 2.5 ULN, omit capecitabine until liver function recovers.

Non-Haematological Toxicities:

Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.

Capecitabine toxicities may be managed symptomatically, with modification of the dose (treatment interruption or dose reduction) according to the information below. Once the dose has been reduced, it should not be increased at a later time. Capecitabine doses omitted for toxicity are not replaced or restored.

See below for capecitabine dose adjustment table:

Capecitabine Dose Adjustment Guidelines for Non-Haematological Toxicities

Common Toxicity Criteria	During Course of Therapy	Dose adjustment for next cycle (% of start dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2: 1st Appearance	Interrupt until resolved to Grade 0 – 1	Give 100% dose, except if PPE give 85% dose*
Grade 2: 2nd Appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 2: 3rd Appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 2: 4th Appearance	Discontinue treatment permanently	
Grade 3: 1st appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose, except if PPE give 70% dose*
Grade 3: 2nd appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 3: 3rd appearance	Discontinue treatment permanently	
Grade 4: 1st appearance	Discontinue permanently **or, with Consultant approval,** interrupt until resolved to Grade 0 – 1	Give 50% dose

* If PPE Grade 2 – 3 occurs for the first time after 10 weeks, interrupt capecitabine. On resolution of toxicity to Grade 0 - 1, capecitabine may be re-introduced with NO dose reduction.

References:

Adapted from the following references:
Sumpter, K et al; Br J Cancer 2005; 92: 1976-1983 (interim analyses of REAL-2 demonstrating equivalence of capecitabine and 5FU)
Cunningham, D et al; Proc ASCO 2006 Abstract LBA4017 (final results of REAL-2)
Cunningham, D et al; NEJM 2006; 355: 11-20 (peri-operative use of ECF)