E – CARBO – X

For patients with locally advanced (inoperable) or metastatic oesophageal or gastric cancer, and who are not suitable for cisplatin;
For peri-operative use in oesophageal or gastric cancer, in patients not suitable for cisplatin
An option for adenocarcinoma of unknown primary
2nd line chemotherapy in metastatic hormone-resistant prostate cancer, particularly for disease refractory to docetaxel

Drug/Dosage:	Epirubicin*	50mg/m^2	IV Day 1
	Carboplatin	AUC 5	IV Day 1
	Capecitabine	625mg/m^2	PO BD continuous throughout treatment

*In upper GI cancer, epirubicin may be omitted, only if specified by Consultant, for patients with poor PS, those who do not wish to lose their hair[1], those with poor cardiac function as specified below, and those where a platinum doublet is more appropriate (e.g. patients receiving a platinum-based re-challenge, and those where a high response rate to systemic treatment is not required)

Administration: Capecitabine tablets (available as 500mg and 150mg) should be swallowed whole with water within 30 minutes after a meal.
Information is available via pharmacy regarding dispersing the tablets 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: *Upper GI cancers:*
Advanced / metastatic use: 3 weekly cycle for 6 - 8 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
Prostate cancer:
3 weekly cycle for up to 6 cycles

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	Day 1
	LFTs	Day 1
	U&Es	Day 1
	EDTA	prior to 1st cycle
	MUGA scan/echo	see Comments
	PSA	Day 1, for prostate cancer patients only

Reason for Update: prostate indication added; WBC cut-off removed; dose modifications advice amended	Approved by Consultant: Dr M Hewish
Version: 5	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 4	Date: 12.10.17
Prepared by: S Taylor	Checked by: C Tucker

Comments:

Maximum cumulative dose of epirubicin = 950mg/m^2
A baseline MUGA scan/echo should be performed where the patient is considered at risk of having significantly impaired cardiac contractility. If ejection fraction is less than 50%, epirubicin should be omitted. 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)
Cycle 1 may be given using the Cockcroft and Gault formula to predict creatinine clearance if the EDTA is not yet available. When using C&G, a "cap" of 125 ml/min should be used for carboplatin dose calculations.
Carboplatin dose should be re-calculated using the EDTA result for subsequent cycles (do not "cap"). EDTA should only be repeated if there is a 30% change in serum creatinine.

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:	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, or more than one 1 week delay, **either** give epirubicin at 75% dose and carboplatin AUC 4; **or** give epirubicin at 50% dose and maintain the carboplatin at AUC 5. If in doubt, discuss with Consultant.

If there is a > 2 week delay, **either** give epirubicin and carboplatin at 50% dose; **or** omit the epirubicin from further cycles, and maintain carboplatin at AUC4/5. If in doubt, discuss with Consultant.

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.

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:
Cunningham, D et al; NEJM 2008; 358: 36 – 46 (REAL-2)
Cunningham, D et al; NEJM 2006; 355: 11-20 (peri-operative use of ECF)
[1]Wagner, A et al; JCO 2006; 24 (18) : 2903 - 2909
Birtle, AJ et al; Br J Cancer 2004; 91 (8): 1472 – 1476 (prostate)
Spicer, J et al; Prostate Cancer Prostatic Dis 2005; 8 (4): 364 - 368