CISPLATIN & CAPECITABINE + RADIOTHERAPY

Oesophageal Cancer – for treatment of localised disease

Drugs/Dosage:	Cisplatin	60mg/m^2	IV	every 3 weeks x 4 doses
	Capecitabine	625mg/m^2 BD	PO	start on the evening of Day 1 and take continuously throughout treatment for a total of 12 weeks

Radiotherapy: 50Gy over 25 fractions (2Gy/#) on Mondays to Fridays, starting at the beginning of Week 7 (Day 43). On days when cisplatin is given, cisplatin should have been running for at least one hour before RT administered (no reference, but local practice)

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 tablets for those patients with swallowing difficulties or with feeding tubes.
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
Mannitol 20% 100ml IV over 15 minutes
Cisplatin in 1 litre 0.9% sodium chloride IV over 2 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hrs
500ml 0.9% sodium chloride IV **or** 500ml - 1 litre water orally over 1 hour

Frequency: 4 cycles of cisplatin chemotherapy, on a 3 weekly cycle
Capecitabine continuous twice daily treatment for 12 weeks
Radiotherapy is to be given during Weeks 7 - 12.

Main Toxicities: myelosuppression; neuropathy / ototoxicity; stomatitis/mucositis; diarrhoea; coronary artery spasm (uncommon); dysphagia; nephrotoxicity; palmar/plantar erythema; ovarian failure/infertility

Anti- emetics: cisplatin: highly emetogenic
capecitabine: mildly emetogenic

Extravasation: non –vesicant

Regular Investigations:	FBC	weekly during RT, & before each cisplatin dose
	U&Es & LFTs	before each cisplatin dose
	Mg^{2+} and Ca^{2+}	before each cisplatin dose
	EDTA	prior to 1st cycle

Comments: For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. Cisplatin dose should be adjusted if necessary once EDTA available. EDTA should only be repeated if result is borderline at start of treatment or if there is a 30% change in serum creatinine.

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml sodium chloride 0.9% IV +/- furosemide 20 - 40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5

litres, a weight gain of 1.5kg or symptoms of fluid overload. The patient should be asked to drink 2 litres of fluid in the 24hrs following cisplatin administration.

Check electrolytes – additional supplementation of magnesium, calcium or potassium may be required.

Dose Modifications

Haematological Toxicity:	Neutrophils ≥ 1.0 x 10^9/l and Platelets ≥ 75 x 10^9/l	Proceed with chemotherapy, including any dose reductions according to haem and non-haem toxicities below:
	Neutrophils 0.5 – 0.9 x 10^9/l or Platelets 50 - 74 x 10^9/l or Any episode of neutropenic sepsis	Stop capecitabine and delay cisplatin until recovery. Once recovered, restart with 75% doses of both cisplatin and capecitabine.
	Neutrophils < 0.5 x 10^9/l or Platelets < 50 x 10^9/l	Stop capecitabine and delay cisplatin until recovery. Once recovered, restart with 50% doses of both cisplatin and capecitabine.

Non-Haematological Capecitabine 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.

Toxicity due to capecitabine may be managed symptomatically and/or modification of the dose (treatment interruption or dose reduction). Use the table below for dose adjustment guidelines. Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

Non-Haematological Dose Adjustment Guidelines for Capecitabine according to CTC

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
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
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

*Grade 2 PPE defined as painful erythema/swelling of hands or feet and/or discomfort affecting daily activities.
Grade 3 PPE defined as moist desquamation, ulceration, blistering and severe pain, such that patient unable to work or perform daily activities.

Renal Impairment: Before every cycle, creatinine clearance should be calculated using Cockcroft and Gault. If borderline, an EDTA should be requested.

If significant renal toxicity, this must be discussed with the Consultant.
NB. Cisplatin is both eliminated primarily (> 90%) in the urine and is itself nephrotoxic.

GFR (ml/min)	Cisplatin Dose
≥ 60	Give 100% dose
45 – 59	Give 75% dose
20 - 44	Cisplatin contra-indicated Carboplatin AUC 5, administered in 250ml 5% glucose over 30 minutes, may be substituted. It may be given according to this protocol, with however no requirement for pre- or post-hydration, nor fluid balance/urine monitoring
< 20	Carboplatin contraindicated

Carboplatin dose should be calculated using the Calvert Formula:
Dose = Target AUC x (25 + GFR)

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

Hepatic Impairment: Bilirubin > 3 x ULN
or
ALT/AST > 2.5 ULN
Omit capecitabine until liver function recovers

Cardiotoxicity: Has been associated with fluoropyrimidine therapy (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. If chest pain does occur, stop capecitabine, perform ECG and measure cardiac enzymes.

Other Toxicities: Seek further advice if patient reports symptoms indicative of neurotoxicity or ototoxicity.

References: Crosby, T et al; Lancet 2013; 14: 627 - 637