

CISPLATIN & CAPECITABINE + RADIOTHERAPY

Oesophageal Cancer – for treatment of localised disease

Drugs/Dosage:	Cisplatin 60mg/m ² IV Capecitabine 625mg/m ² BD PO	every 3 weeks x 4 doses starting on the evening of Day 1 and taken 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 MgSO 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 U&Es & LFTs Mg ²⁺ and Ca ²⁺ EDTA	Weekly during RT, & before each cisplatin dose before each cisplatin dose before each cisplatin dose Prior to 1 st 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.

Reason for Update: New protocol as alternative to Herskovic	Approved by Lead Chemotherapy Nurse: C Palles-Clark
Version: 1	Approved by Consultant: Dr S Cummins
Supersedes: None	Date: 18.1.08
Prepared by: S Taylor	Checked by: S Seymour

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

Dose Modifications

Haematological Toxicity:	Neutrophils $\geq 1.0 \times 10^9/l$ and Platelets $\geq 75 \times 10^9/l$	Proceed with chemotherapy, including any dose reductions according to haem and non-haem toxicities below:
	Neutrophils $0.5 - 0.9 \times 10^9/l$ or Platelets $50 - 74 \times 10^9/l$ 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 $< 0.5 \times 10^9/l$ or Platelets $< 50 \times 10^9/l$	Stop capecitabine and delay cisplatin until recovery. Once recovered, restart with 50% doses of both cisplatin and capecitabine.
	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: 1 st Appearance	Interrupt until resolved to Grade 0 – 1	Give 100% dose
Grade 2: 2 nd Appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 2: 3 rd Appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 2: 4 th Appearance	Discontinue treatment permanently	
Grade 3: 1 st appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 3: 2 nd appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 3: 3 rd appearance	Discontinue treatment permanently	
Grade 4: 1 st 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.

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Renal Impairment: 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%
50 – 60	Give 75%
40 – 50	Give 50%
< 40	Cisplatin contra-indicated

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

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: Scope 1 trial, NCRI Upper GI Clinical Studies Group, Version 2.0, 2007

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