Systemic Anti Cancer Therapy Protocol

Cisplatin and Capecitabine + XRT (SCOPE trial protocol) Oesophageal Cancer

PROTOCOL REF: MPHACCXGA
(Version No: 1.0)

Approved for use in:

- Locally advanced or inoperable carcinoma of the oesophagus

Dosage:

Drug	Dose	Route	Frequency
Cisplatin	**60 mg/m^2**	IV infusion	Day 1 only of a 21 day cycle
Capecitabine	**625 mg/m^2**	Oral	Twice Daily on days 1-21 of a 21 day cycle

Maximum 4 cycles (2 cycles concurrent with radiotherapy)

Administration and Counselling Points:

Capecitabine

- Capecitabine is available in 150mg and 500mg tablets
- Tablets should be taken 12 hours apart, morning and evening. Swallow whole with water within 30 minutes of a meal
- Continue according to the treatment plan and stop taking on the originally scheduled day. Take missed doses if remembered within 2 hours of the normal scheduled time. Otherwise continue with the next scheduled dose. Do not double up missed doses
- In case of swallowing difficulties the tablets may be dissolved in 200ml warm water. Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only

Cisplatin

- Review patients fluid intake over the previous 24 hours
- Ensure renal function is calculated and checked before commencing treatment

- Weigh the patient before commencing IV hydration
- Monitor fluid balance throughout treatment (input and output)

Emetogenic risk:

Severely emetogenic

Supportive treatments:

- Aprepitant 125mg one hour before chemotherapy, 80mg on days 2 and 3
- Dexamethasone 4mg twice a day for 3 days
- Domperidone 10mg three times a day when required
- Loperamide 2mg when required

Extravasation risk:

Cisplatin – *Irritant* - apply warm compress to affected area for 20 mins to disperse and dilute 4 times a day for 24-48 hours. Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries' for further information

Dosing in renal and hepatic impairment:

Renal	Cisplatin	• CrCl 50-59 ml/min: 75% of the original dose • CrCl 40-49 ml/min: 50% of the original dose • CrCl < 40 ml/min: not recommended (consider switching to carboplatin)
	Capecitabine	• CrCl 51-80 ml/min: no dose adjustment required • CrCl 30-50 ml/min: 75% of the original dose • CrCl <30 ml/min: not recommended

Hepatic	Cisplatin	No dose adjustments required
	Capecitabine	No dose adjustments required

Interactions:

Warfarin/coumarin anti-coagulants – can increase anticoagulant effect. Avoid if possible or consider switching patient to a LMWH during treatment.

Phenytoin - Capecitabine may increase the serum concentration of phenytoin. Cisplatin may reduce the serum level of phenytoin (probably due to reduced absorption and/or increased metabolism). For patients taking phenytoin, serum levels should be monitored along with checking response to therapy and adjust the dose accordingly.

Folinates – can enhance the toxicity of capecitabine. Avoid concomitant use of folinic and folic acid.

Nephrotoxic drugs - Concomitant administration of nephrotoxic drugs (e.g. cephalosporins, aminoglycosides, or contrast media) will potentiate the toxic effect of cisplatin on the kidneys.

Loop diuretics – concomitant use with cisplatin should be approached with caution due to cumulative nephrotoxicity and ototoxicity.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant**	**125mg**	**PO**	60 mins before chemotherapy
	Dexamethasone	**12mg**	**PO**	30 mins before chemotherapy
	Ondansetron	**24mg**	**PO**	30 mins before chemotherapy
	Furosemide	**20mg**	**PO**	Before cisplatin pre-hydration
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		**IV over 90 minutes**	
	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes** **If urine output still not adequate contact the urology team**			
	Cisplatin	**60 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		**IV over 90 minutes**	
1 to 21	**Capecitabine**	**625 mg/m^2**	**PO**	Twice a day (morning and evening)

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, stomatitis, alopecia

Cisplatin
Nephrotoxicity, ototoxicity and neuropathy
Capecitabine
Abdominal pain, dyspepsia, rash, dry skin, pruritus, hyperpigmentation, palmer-plantar erythema, insomnia, depression, headache, dizziness. Elevated liver function tests. Cardiotoxicity (including myocardial infarction, angina and arrhythmias).

DPD deficiency – leads to severe early 5FU toxicity, affects approximately 3-6% of population, may be life threatening in up to 1% of cases.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X					
Clinical Assessment	X			X		As clinically indicated, prior to commencing concurrent radiotherapy or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	Every cycle
Dihydropyrimidine dehydrogenase (DPD) deficiency	X					This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
CT scan	X					At the end of treatment
ECG	X					If clinically indicated
Blood pressure measurement	X					Repeat if clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
Blood glucose	X					Repeat if clinically indicated
Height	X					

During treatment and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Common Toxicity Criteria	Dose changes within a treatment cycle	Dose adjustment for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
• 1st appearance	Interrupt until resolved to grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue treatment	
Grade 3		
• 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue treatment	
Grade 4		
• 1st appearance	Discontinue permanently **or** If clinician deems it to be in patients best interest to continue, interrupt until resolved to grade 0-1	50%
• 2nd appearance	Discontinue treatment	

References:

1. https://www.medicines.org.uk/emc
2. Hurt CN et al. SCOPE1: a randomised phased II/III multicentre clinical trial of definitive chemoradiation, with or without cetuximab, in carcinoma of the oesophagus. BMC Cancer 11, article number: 466 (2011)
3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08