Systemic Anti Cancer Therapy Protocol

Cisplatin and Fluorouracil (5-FU) Oesophageal/GOJ Cancer

PROTOCOL REF: MPHACF5GA
(Version No: 1.0)

Approved for use in:

- Neoadjuvant treatment for oesophageal or gastro-oesophageal junction carcinoma
- Locally advanced or inoperable oesophageal carcinoma

Dosage:

Drug	Dose	Route	Frequency
Cisplatin	**80 mg/m^2**	IV infusion	Day 1 only of a 21 day cycle
Fluorouracil (5-FU)	**1000 mg/m^2/24 hours**	IV infusion	Days 1-4 of a 21 day cycle

Maximum 2 cycles (neoadjuvant) or 4-6 cycles for advanced

Administration and Counselling Points:

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 and before and after cisplatin infusion
- Monitor fluid balance throughout treatment (input and output). Give furosemide 20-40mg if there is a positive fluid balance of 1.5L, weight gain of 1.5kg or symptoms of fluid overload
- Patients should be advised to drink 2L of fluid over 24 hours after cisplatin infusion and to contact triage immediately if unable to do so for any reason

Fluorouracil

- 5FU can be administered as either;
  - INPATIENT – 4 x 24hr fluorouracil infusions
  - OUTPATIENT – via a 96-hour LV2 pump (will require PICC line insertion)

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.

Fluorouracil – *Irritant* - apply cold 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
	Fluorouracil	No dose adjustments required

Hepatic	Cisplatin	No dose adjustments required	
	Fluorouracil	Mild to moderate hepatic impairment without renal impairment:	no dose adjustments required
		Severe; **One** of Bilirubin > 1.5 x ULN **Or** AST/ALT > 10 x ULN **Or** AlkP > 6 x ULN	Not recommended

Interactions:

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

Phenytoin - Fluorouracil 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.

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:

<table>
<tr><th>Day</th><th>Drug</th><th>Dose</th><th>Route</th><th>Diluent and rate</th></tr>
<tr><td rowspan="9">1</td><td>Aprepitant</td><td>125mg</td><td>PO</td><td>60 mins before chemotherapy</td></tr>
<tr><td>Dexamethasone</td><td>12mg</td><td>PO</td><td>30 mins before chemotherapy</td></tr>
<tr><td>Ondansetron</td><td>24mg</td><td>PO</td><td>30 mins before chemotherapy</td></tr>
<tr><td>Furosemide</td><td>20mg</td><td>PO</td><td>Before cisplatin pre-hydration</td></tr>
<tr><td colspan="2">Sodium Chloride 0.9% 1000mL
With 20mmol Potassium Chloride</td><td colspan="2">IV over 90 minutes</td></tr>
<tr><td colspan="4">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 medical team</td></tr>
<tr><td>Cisplatin</td><td>80 mg/m²</td><td>IV</td><td>Sodium Chloride 0.9% 1000mL over 90 minutes</td></tr>
<tr><td colspan="2">Sodium Chloride 0.9% 1000mL
With 20mmol Potassium Chloride</td><td colspan="2">IV over 90 minutes</td></tr>
<tr style="display:none"></tr>
<tr><td>1 to 4</td><td>Fluorouracil</td><td>1000 mg/m²/24 hours</td><td>IV</td><td>Continuous infusion over 4 days*</td></tr>
</table>

*see administration notes for options of how to administer

Main toxicities:

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

Cisplatin
Nephrotoxicity, ototoxicity and neuropathy
Fluorouracil
Dyspepsia, rash, dry skin, pruritus, hyperpigmentation, palmer-plantar erythema, insomnia, headache, dizziness. 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 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	X	X	X	X	Every cycle
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.

If longer than one week delay, give **75% dose of cisplatin and 5FU** for the second cycle.

Non- Haematological toxicity:

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

References:

1. https://www.medicines.org.uk/emc
2. Allum WH et al. Long-term results of a randomised trial of surgery with or without preoperative chemotherapy in oesophageal cancer (OEO2). Journal of Clin. Onc. 27, no.30 (October 2009) 5062-5067
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