CISPLATIN & 5 FLUOROURACIL

1. First-line palliative use in advanced squamous cell carcinoma of anus or oesophagus
2. May occasionally be used in patients with upper GI adenocarcinoma and who are unable to tolerate capecitabine as part of (E)CX or (E)CarboX
3. Neo-adjuvant use in squamous cell carcinoma of the oesophagus

Drugs/Dosage:	Cisplatin	80mg/m^2	IV	Day 1
	5-Fluorouracil	1000mg/m^2/24hr	IV	Day 1 – Day 4

N.B. Elderly/frail patients may require 5FU and cisplatin doses to be given at 75% of the above, or substitution of cisplatin with carboplatin AUC 4 - 5, as specified by Consultant.

Administration:
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 3 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
500ml sodium chloride 0.9% IV **or** 500mls – 1 litre water orally over 1 hour.

5 Fluorouracil continuous IV infusion over 4 days, via CVC and ambulatory infusion device. This may be attached on the afternoon of Day 1, after the cisplatin and post-hydration have completed.
If patient considered not suitable for central line: 5FU may be given as a continuous peripheral IV infusion over 4 days (as an in-patient), in 4 x 1 litre 0.9% sodium chloride. Cisplatin, hydration and any other IV drugs are to be given via a second peripheral cannula.

Frequency:
3 weekly cycle
Palliative use: 6 cycles (for patients with continuing response and excellent tolerability, consideration could be given to consolidating to a maximum of 8 cycles)
Neo-adjuvant: 2 cycles only, prior to surgery planned 3-5 weeks after last cisplatin

Main Toxicities:
myelosuppression; neuropathy / ototoxicity; stomatitis; diarrhoea; coronary artery spasm (see Comments); nephrotoxicity; palmar / plantar erythema; alopecia (mild); ovarian failure / infertility

Anti- emetics:
Day 1: highly emetogenic, including aprepitant
Days 2 – 4: moderately emetogenic

Extravasation:
non -vesicants

Regular Investigations:	FBC	Day 1
	LFTs	Day 1
	U&Es	Day 1
	Mg^{2+} and Ca^{2+}	Day 1
	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 the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Reason for Update: merged with upper GI protocol; indications and number of cycles reviewed; WBC cut-off removed; aprepitant added	Approved by Consultant: Dr M Hewish
Version: 5	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 4 anal, and Version 7 oesophagus	Date: 7.12.17
Prepared by: S Taylor	Checked by: C Tucker

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

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 treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the 5FU should be withdrawn permanently.[1] Refer to Consultant to discuss.

Dose Modifications

Haematological Toxicity:	Neutrophils < 1.5 x 10^9/l or Platelets < 100 x 10^9/l	Delay chemotherapy for 1 week. Repeat FBC and, if normal, resume at full dose. If there is a 2 week delay, give both drugs at 75% dose. If there is a > 2 week delay, give both drugs at 50% dose.

Renal Impairment: In neo-adjuvant setting, if GFR < 60ml/min, discuss with Consultant before proceeding – it is imperative that patients going to surgery do not have significant reduction in renal function.

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

GFR (ml/min)	Cisplatin Dose
≥ 60	Give 100% dose
45 - 59	Give 75% dose
44 – 20	Cisplatin contra-indicated Carboplatin AUC 5, administered in 250ml 5% Glucose over 30-60 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 contra-indicated

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

Hepatic Impairment:

Moderate hepatic impairment	Reduce initial 5FU dose by 1/3
Severe hepatic impairment	Reduce initial 5FU dose by ½

Dose can be increased if no toxicity seen. If in doubt, check with the relevant Consultant.

Other Toxicities: If Grade 3/4 mucositis, diarrhoea or PPE occurs, the dose of 5FU should be reduced to 750mg/m^2/24 hours in subsequent cycles.
For any Grade 4 toxicity, discuss with Consultant before proceeding.

Seek further advice if the patient reports symptoms indicative of neurotoxicity or ototoxicity.

References:

Meadows, HM et al, on behalf of UKCCCR Anal Cancer Trial Working Party; British Journal of Cancer 1997; 76 Suppl 1; O33: 25
ACT II study, Cancer Research UK Jan 2002
[1]COIN Guidelines, October 2000
Neo-adjuvant: MRC Oesophageal Cancer Working Party, Lancet 2002; 359: 1727–1733

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