CISPLATIN AND 5-FLUOROURACIL

1. Neo-adjuvant use in Cancer of the Oesophagus
2. Post-operative adjuvant use in patients who did not receive chemotherapy before surgery

Drugs/Dosage:	Cisplatin	80mg/m^2	IV	D1
	5 Fluorouracil	1000mg/m^2/24hr	IV	D1 – D4

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 $MgS0_4$ IV over 2 hrs
500ml 0.9% Sodium Chloride IV **or** 500ml - 1 litre water orally over 1 hour

For patients with central line:
5 Fluorouracil continuous IV infusion over 4 days, given 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:
5-Fluorouracil to 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 to be given via a second peripheral cannula.

Frequency:

3 weekly cycle
Neo-adjuvant: 2 cycles only, prior to surgery planned 3-5 weeks after last cisplatin
Adjuvant: 2 cycles

Main Toxicities:

myelosuppression; neuropathy / ototoxicity; mucositis; diarrhoea; coronary artery spasm (see Comments); nephrotoxicity; palmar/plantar erythema; ovarian failure/Infertility

Anti- emetics:

Day 1: highly emetogenic
Days 2 – 4: IV antiemetics not routinely required; regular oral dexamethasone and metoclopramide (as moderately emetogenic) is first-line treatment

Extravasation:

non -vesicants

Regular Investigations:	FBC	D1
	LFTs	D1
	U&Es	D1
	Mg^{2+} and Ca^{2+}	D1
	EDTA (see Comments)	Prior to 1st cycle

Comments:

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.

For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. **However, if borderline, discuss with Consultant before proceeding.** 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.

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 cisplatin administration.

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:	WBC < 3.5 x 10^9/l or Neutrophils < 1.5 x 10^9/l or Platelets < 100 x 10^9/l	Delay by 1 week. Repeat FBC and, if within normal limits, continue with 75% dose of both cisplatin and 5FU. If after 1 week the result is not satisfactory, delay for a 2nd week, then continue with 50% doses of both cisplatin and 5FU.

Renal Impairment: NB. Cisplatin is both eliminated primarily (> 90%) in the urine and is itself nephrotoxic. **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.

GFR (ml/min)	Cisplatin Dose
> 60	Give 100%
50 – 60	Give 75%
40 – 50	Give 50%
39 - 20	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)

Hepatic Impairment:

Moderate hepatic impairment	Reduce initial 5FU dose by ⅓
Severe hepatic impairment	Reduce initial 5FU dose by ½

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

Other Toxicities: If Grade 3/4 mucositis, diarrhoea or PPE occurs, the dose of 5FU should be reduced to 750mg/m^2/24hr for second cycle. Seek further advice if the patient reports symptoms indicative of neurotoxicity or ototoxicity.

References: Neo-adjuvant: MRC Oesophageal Cancer Working Party, Lancet 2002; 359: 1727–1733
Adjuvant: Ando, N et al; JCO (2003); 21; 24: 4592 - 4596
[1]COIN Guidelines, Oct 2000