CISPLATIN & 5 FLUOROURACIL

1. Loco-regional or metastatic recurrence of H&N SCC after radical surgery or radiotherapy, only for those patients who are not suitable or eligible for chemotherapy in combination with cetuximab
2. Neo-adjuvant treatment in nasopharyngeal H&N cancer
3. Neo-adjuvant use in SCC H&N pre-RT where TPF not suitable or approved

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

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
5 Fluorouracil continuous IV infusion over 4 days, given via central venous catheter and ambulatory infusion device

Frequency:	Recurrence of SCC:	3 weekly cycle for 6 cycles
	Neo-adjuvant use:	3 weekly cycle for 2 - 3 cycles

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

Anti- emetics: Day 1: highly emetogenic

Extravasation: non -vesicants

Regular Investigations:	FBC	Day 1
	LFTs and U&Es	Day 1
	Mg^{2+} and Ca^{2+}	Day 1
	EDTA	prior to 1st cycle

Comments: If patient has any baseline hearing problems, carboplatin AUC 5 should be substituted for cisplatin, administered as discussed below under Renal Impairment.

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.

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.

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

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 and Platelets ≥ 100 x 10^9/l	Proceed with treatment.
Neutrophils 0.5 - 1.4 x 10^9/l or Platelets 75 - 99 x 10^9/l	Delay by 1 week. Repeat FBC and, if within normal parameters, continue with full dose treatment.
Neutrophils < 0.5 x 10^9/l or Platelets < 75 x 10^9/l	Delay by 1 week. Repeat FBC and, if within normal parameters, continue with 80% doses of both cisplatin and 5FU.

If any episode of neutropenic sepsis, give all further cycles of chemotherapy with a 20% dose reduction of both cisplatin and 5FU.

Renal Impairment:

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 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 Consultant.

Other Toxicities:

If Grade 3/4 mucositis, diarrhoea or PPE occurs, the dose of 5FU should be reduced to 750mg/m^2/24hrs in subsequent cycles.
Seek further advice if the patient reports symptoms indicative of neurotoxicity or ototoxicity.

References:

Originally modified from OE02 Trial Protocol, MRC (1992)
Vermorken, JB et al; NEJM 2008; 359 (11): 1116 - 1127 [1]COIN Guidelines, Oct 2000