TPF

Induction chemotherapy in H&N SCC, for suitable patients who have locally advanced unresectable disease, prior to chemo-radiotherapy with carboplatin

Drugs/Dosage:	Docetaxel	75mg/m^2	IV	Day 1
	Cisplatin	100mg/m^2	IV	Day 1
	5 Fluorouracil	1000mg/m^2/24hr	IV	Days 1 – 4 (96 hours)

G-CSF primary prophylaxis for 5 days, starting on Day 6 (no earlier than 24 hours after chemotherapy completed)

Pre-medication: Dexamethasone 8 mg po bd for 3 days, commencing the morning of the day prior to docetaxel chemotherapy, to prevent hypersensitivity reactions and fluid retention.
If the patient has not taken the oral pre-med for any reason, intravenous dexamethasone is not recommended and can only be substituted if prescribed by a Consultant.

Administration: Docetaxel in 250ml 0.9% sodium chloride over 1 hour (compatible at the Y-site with the pre-hydration fluid)
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 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hours

5 Fluorouracil continuous IV infusion over 4 days, given **via central venous catheter** and ambulatory infusion device (to be attached at the end of Day 1)

Frequency: 3 weekly cycle for up to 3 cycles,
followed by chemo-radiotherapy using the Carboplatin AUC 1.5 & RT protocol

Main Toxicities: myelosuppression; neuropathy / ototoxicity; mucositis; alopecia; diarrhoea; coronary artery spasm (see Comments); nephrotoxicity; palmar-plantar erythema; fluid retention; myalgia/arthralgia; docetaxel infusion-related reactions (↑ risk with 1st/2nd treatment); skin reactions & nail changes; ovarian failure/infertility

Anti- emetics: highly emetogenic, including aprepitant
(note: requires an additional 4mg dexamethasone pre cisplatin on top of oral dexamethasone pre-med for docetaxel, plus dex 4mg bd on Days 3 and 4, once 8mg bd course is completed)

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

Reason for Update: antiemetic dex wording; changed to all cisplatin given on Day 1; primary G-CSF added, and cipro removed	Approved by Consultant: Dr S Whitaker
Version: 3	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 2	Date: 6.5.15
Prepared by: S Taylor	Checked by: C Tucker

Comments: Offer scalp cooling.

If patient has any baseline hearing problems, discuss with Consultant;
Carboplatin AUC 5, on Day 1 only, may be substituted for cisplatin, administered in 250ml 5% glucose over 30 minutes. It may be given according to this protocol, with however no requirement for pre- or post-hydration, nor fluid balance/urine monitoring

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:	WBC < 3.0 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 parameters, proceed, with consideration of 25% dose reduction of all drugs for remaining cycles. If, after 1 week, the FBC is still not satisfactory, delay for a second week and discuss with Consultant.

If patient has febrile neutropenia or neutrophils < 0.5 x 10^9/l for more than 1 week, the dose of docetaxel should be reduced to 60mg/m^2 for remaining cycles.
In the case of any Grade 4 thrombocytopenia (platelets < 25 x 10^9/l), docetaxel dose should be reduced to 60mg/m^2.

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
< 45	Cisplatin contra-indicated & this regimen not recommended

Hepatic Impairment: Bilirubin > 22 μmol/l
or
ALT/AST > 3.5 x ULN
with
ALP > 6 x ULN

Docetaxel not recommended - may only be administered with consultant approval

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:

For Grade 3 diarrhoea: first episode, reduce 5FU dose by 20%
second episode, also reduce docetaxel by 20%

For Grade 4 diarrhoea: first episode, reduce 5FU and docetaxel by 20%
second episode, discontinue treatment

For Grade 3 mucositis: first episode, reduce 5FU dose by 20%
second episode, stop 5FU in any remaining cycles
third episode, reduce docetaxel dose by 20%

For Grade 4 mucositis: stop 5FU for remaining cycles
second episode, also reduce docetaxel dose by 20%

If Grade 3/4 PPE occurs, consider reducing the dose of 5FU in subsequent cycles – discuss with consultant, as no specific dose reduction advice is given in the pivotal reference.

If Grade 3 or 4 cutaneous reactions, once patient recovered, reduce docetaxel dose to 60mg/m^2. If symptoms return, stop docetaxel.

Seek further advice regarding use of cisplatin if the patient reports symptoms indicative of neurotoxicity or ototoxicity.
If Grade 2 neuropathy, reduce docetaxel dose to 60mg/m^2. If symptoms return, stop docetaxel. If Grade 3 or 4 neuropathy, discontinue docetaxel.

Myalgia / arthralgia due to docetaxel: often co-exist, usually Grade 1 or Grade 2. Management consists of reassuring patients that it is self-limiting. Consider use of NSAIDs, although not always effective.

References:

Posner et al; NEJM 2007; 357 (17): 1705 - 1715
[1]COIN Guidelines, October 2000