CISPLATIN / 5-FLUOROURACIL + RADIOTHERAPY (HERSKOVIC)

Oesophageal Cancer – for treatment of localised disease

Drugs/Dosage:

5-Fluorouracil 1000mg/m^2/24hr IV D1 – D4 of Weeks 1, 5, 8 & 11*
Cisplatin 75mg/m^2 IV D1 of Weeks 1, 5, 8 & 11*
RT: 50Gy over 25 fractions (2Gy/#) on Mondays to Fridays of Weeks 1-5 inclusive*

***To reduce delay due to radiotherapy waiting times, an alternative schedule is:**
5-Fluorouracil 1000mg/m^2/24hr IV D1 – D4 of Weeks 1, 4, 8 & 11
Cisplatin 75mg/m^2 IV D1 of Weeks 1, 4, 8 & 11
RT: 50Gy over 25 fractions (2Gy/#) on Mondays to Fridays of Weeks 4-8 inclusive

Radiotherapy:

Cisplatin must have been running for at least one hour before RT administered on Day 1 but it is not necessary for 5FU to have been initiated; 5FU must be initiated on the afternoon of Day 1 in readiness for RT doses during the remainder of the week (no reference, but SE request March 2006)

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:

4 cycles of chemotherapy, starting at the beginning of Weeks 1, 5, 8 and 11
Radiotherapy is to be given during Weeks 1 – 5 inclusive.
or, to reduce delay due to RT waiting times,
4 cycles of chemotherapy, starting at the beginning of Weeks 1, 4, 8 and 11
Radiotherapy is to be given during Weeks 4 – 8 inclusive

Main Toxicities:

myelosuppression; neuropathy / ototoxicity; stomatitis/mucositis; diarrhoea; coronary artery spasm (see Comments); dysphagia; 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	Weekly during RT, & D1 of Weeks containing chemotherapy
LFTs	D1 of Weeks containing chemotherapy
U&Es	D1 of Weeks containing chemotherapy
Mg^{2+} and Ca^{2+}	D1 of Weeks containing chemotherapy
EDTA	Prior to 1st cycle

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Version: 5	Approved by Consultant: Dr S Essapen
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Prepared by: S Taylor	Checked by: S Punter

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 result is borderline at 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 cisplatin administration.

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: **NB. As this is potentially curative, chemotherapy should not be delayed. If patient presents with low blood counts, do not defer but continue with doses according to the advice below, followed by G-CSF rescue (starting on Day 5 of the cycle) if appropriate.**

Neutrophils 1.0 – 1.5 x 10^9/l or Platelets 50 - 74 x 10^9/l	Give 75% cisplatin dose and full dose 5FU for this cycle. Review dose again on each cycle, according to FBC.
Neutrophils < 1.0 x 10^9/l or Platelets < 50 x 10^9/l	Give 50% cisplatin dose and full dose 5FU for this cycle. Review dose again on each cycle, according to FBC.

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

GFR (ml/min)	Cisplatin Dose
> 60	Give 100%
50 – 60	Give 75%
40 – 50	Give 50%
< 40	Cisplatin contra-indicated

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 the relevant Consultant.

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

References: Herskovic, A. et al; NEJM; Vol 326: 1593 – 1598; [1]COIN Guidelines, Oct 2000

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