CISPLATIN (WEEKLY) & PVI 5FU & RADIOTHERAPY

Chemo-radiotherapy for use in **adenocarcinoma** of the cervix, vagina or vulva, where surgery not appropriate due to stage or co-morbidity

Drugs/Dosage:	Cisplatin	35 - 40mg/m^2	IV	once weekly during radiotherapy*
	5 Fluorouracil	200mg/m^2/24hrs	IV	continuous throughout radiotherapy**

Radiotherapy: 50.4Gy in 28 fractions (1.8Gy/#) on Mondays to Fridays for 5½ weeks + 2-3# of brachytherapy +/- pelvic side wall boosts up to 9Gy/5#.
RT must commence within 1 hour of the end of cisplatin infusion.
Cisplatin must not be given on the same day as brachytherapy.

Administration: 5FU continuous IV infusion via CVC & ambulatory infusion device
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hours
Mannitol 20% 100ml IV over 15 minutes
Cisplatin in 1 litre 0.9% sodium chloride IV over 2 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hours
500ml 0.9% sodium chloride IV **or** 500ml – 1 litre water orally over 1 hour

Frequency: weekly cisplatin, plus continuous 5FU, during radiotherapy and brachytherapy
(chemotherapy may occasionally start pre-RT in highly symptomatic patients)

Main Toxicities: myelosuppression; alopecia; diarrhoea; mucositis; nephrotoxicity; neuropathy / ototoxicity; palmar/plantar erythema (PPE); coronary artery spasm (see Comments); RT-related side effects; ovarian failure/infertility

Anti-emetics: Cisplatin: highly emetogenic 5-Fluorouracil: mildly emetogenic

Extravasation: non-vesicants

Regular Investigations:	FBC	weekly before each cisplatin dose (N.B. see Haem Toxicity for Hb monitoring)
	U&Es & LFTs	weekly before each cisplatin dose
	Mg^{2+} and Ca^{2+}	weekly before each cisplatin dose
	EDTA	prior to 1st dose of cisplatin

Comments

For patients receiving the first cisplatin dose and the EDTA is not yet available, Cockcroft & Gault formula may be used to calculate creatinine clearance. 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 K^+, Ca^{2+} or Mg^{2+} may be required.

Ensure that patient is reviewed for side effects indicative of neurotoxicity or ototoxicity.

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 +/- 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.

Reason for Update: statement re Hb < 12 added; indications updated	Approved by Consultant: Dr A Stewart
Version: 4	Approved by Lead Chemotherapy Nurse: Sara Wills-Percy
Supersedes: Version 3	Date: 22.9.16
Prepared by: S Taylor	Checked by: C Tucker

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, which is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. Standard investigation & treatment of angina may be required. If rechallenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the 5FU should be withdrawn permanently.

Dose Modifications

Haematological Toxicity:

Neutrophils ≥ 1.5 x 10^9/l and Platelets ≥ 100 x 10^9/l	Proceed with chemo-radiotherapy
Neutrophils 1.0 - 1.4 x 10^9/l or Platelets 50 - 99 x 10^9/l	Delay Cisplatin for 1 week. Continue with 5FU and radiotherapy. Repeat count and, if recovered, resume cisplatin at full dose.
Neutrophils < 1.0 x 10^9/l or Platelets < 50 x 10^9/l	Delay cisplatin and 5FU. RT to continue. Once FBC has recovered, discuss management with Consultant and only re-introduce chemotherapy with Consultant approval

Haemoglobin (Hb) needs to be maintained above 12g/dl throughout treatment. If the Hb falls below this level, a blood transfusion needs to be arranged (treatment may continue).

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

GFR (ml/min)	Cisplatin Dose
≥ 60	Give 100%
45 – 59	Give 75%
20 - 44	Cisplatin contra-indicated Carboplatin AUC 2*, 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

*There is no consensus in the literature regarding the optimum carboplatin dose. This dose reflects SLCC Consultant preference and experience. 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 1/2

Increase dose if no toxicity. If in doubt, check with relevant consultant.

Diarrhoea: Grade 1-2 – standard anti-diarrhoeal drugs can be used but, if diarrhoea persists, stop the 5FU for 1 week and recommence with a 25% dose reduction.

Cutaneous Toxicity: Patients with any grade PPE should receive Pyridoxine 50mgs po tds throughout treatment. For Grade 3 mucositis or PPE, 5FU should be stopped for 1-2 weeks until healing has occurred and recommenced with a 25% dose reduction. Cisplatin will continue at full dose.

Neuropathy: If patient develops Grade 2 neuropathy or ototoxicity, discuss with Consultant.

References: Adapted from: Rose, PG et al, NEJM 1999; 340: 1144 – 1153
Keys, HM et al, NEJM 1999; 340:1154 – 1161
Morris, M et al, NEJM 1999; 340: 1137 - 1143