Accelerated MVAC

Neo-adjuvant use, pre cystectomy or pre chemo-radiotherapy, in transitional cell carcinoma of the bladder, for patients with good performance status and adverse prognostic factors
2nd line palliative use in advanced or metastatic bladder cancer, ureteric cancer or renal pelvis carcinoma

Drugs/Dosage:	Methotrexate	30mg/m^2	IV	Day 1
	Vinblastine	3mg/m^2	IV	Day 1
	Doxorubicin	30mg/m^2	IV	Day 1
	Cisplatin	70mg/m^2	IV	Day 1
	Folinic acid	15mg	po	6hrly x 6 doses, starting 24 hours post MTX
	Primary G-CSF prophylaxis		s/c	once daily for 7 days, starting on Day 4 of the cycle

Administration: Methotrexate as a bolus injection
Vinblastine diluted in 50ml 0.9% sodium chloride and infused over 5-10 minutes
Doxorubicin via fast running infusion of 0.9% Sodium Chloride

Cisplatin:
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 $MgSO_4$ IV over 2 hours
500ml 0.9% sodium chloride IV **or** 500ml-1 litre water orally over 1 hour

Frequency: Repeat every 14 days
Neo-adjuvant use: 3 cycles
Palliative use: up to 6 cycles

Main Toxicities: myelosuppression; nephrotoxicity; cardiomyopathy; constipation; neurotoxicity / ototoxicity; mucositis; alopecia; infertility/ovarian failure

Anti-emetics: highly emetogenic

Extravasation: vinblastine and doxorubicin are vesicants

Regular Investigations:	FBC	Day 1
	U&Es & LFTs	Day 1
	Mg^{2+} and Ca^{2+}	Day 1
	EDTA	Prior to 1st cycle
	MUGA scan	See Comments

Comments: Use with caution if third space fluid or renal impairment, which may reduce MTX clearance.

Maximum cumulative dose of Doxorubicin = 450 - 550 mg/m^2
A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

For patients on Cycle 1 whose EDTA is not yet available, Cockcroft and Gault may be used to predict GFR. Cisplatin and MTX doses 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.

Reason for Update: G-CSF dosing and scheduling reviewed	Approved by Consultant: Dr J Money-Kyrle
Version: 6	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 5	Date: 6.5.15
Prepared by: S Taylor	Checked by: C Tucker

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.

Dose Modifications

Haematological Toxicity:

WBC < 3.0 x 10^9/l or Neutrophils < 1.0 x 10^9/l or Platelets < 100 x 10^9/l	Delay for 1 week. Consider giving more G-CSF appropriate. Repeat FBC and, if within normal parameters, continue with full dose. If history of febrile neutropenia or poor performance status, discuss with Consultant.

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

GFR (ml/min)	Cisplatin Dose
≥ 60	Give 100%
45 – 59	Give 75%
< 45	CI (consider carboplatin)

GFR (ml/min)	Methotrexate Dose*
≥ 60	Give 100%
45	Give 50% **but check with Consultant first**
<30	Omit

* Dose modifications as requested by Dr Money-Kyrle

Hepatic Impairment:

ALT/AST	Bilirubin (µmol/l)	Vinblastine Dose
60 – 180 **or**	26 –51	Give 50% dose
Normal **and**	> 51	Give 50% dose
> 180 **and**	> 51	Discontinue

ALT / AST	Bilirubin (µmol/l)	Doxorubicin Dose
2 – 3 x ULN	-	Give 75%
> 3 x ULN or	20 – 50	Give 50%
	51 – 85	Give 25%
	> 85	Omit

AST	Bilirubin (µmol/l)	Methotrexate Dose
> 180 **or**	51 – 85	Give 75% dose
-	> 85	Do not give

Mucosal Toxicity: For mucositis/stomatitis not related to haematological toxicity, institute appropriate oral hygiene measures. Check renal function (re MTX dose) and consider prolonged course of folinic acid with subsequent cycles, starting 24 hours post methotrexate injection. Dose reduction of MTX should be considered if mucositis is severe.

Neurotoxicity: Seek further advice if the patient reports symptoms indicative of ototoxicity (tinnitus, deafness) or neurotoxicity (paraesthesias, difficulty with motor control).

References:
Sternberg, C et al; JCO (2001); Vol 19 (10): 2638 – 2646
RMH Neo-adjuvant study presented at BAUS 2005 (not published)