Chemotherapy Protocol

BLADDER

CISPLATIN-DOXORUBICIN-METHOTREXATE-VINBLASTINE

(Accelerated MVAC)

Regimen

- Bladder-Cisplatin-Doxorubicin-Methotrexate-Vinblastine (AccMVAC)

Indication

- First or second line treatment of locally advanced or metastatic urothelial cancer
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Doxorubicin	Cardio toxicity, urinary discolouration (red)
Methotrexate	Stomatitis, conjunctivitis, renal toxicity
Vinblastine	Peripheral neuropathy, abdominal pain, constipation, jaw pain

The presence of a third fluid compartment e.g. ascites or renal failure may delay methotrexate clearance hence increase toxicity.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, LFTs and U&Es prior to day one of treatment
- Calculated or measured creatinine clearance prior to each cycle. EDTA may be considered prior to cycle one or if there are significant changes in renal function during treatment.
- Ensure adequate cardiac function before starting treatment. Baseline LVEF should be considered, particularly in patients with a history of cardiac problems or in the elderly.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Day 1

Neutrophils ($x10^9$/L)	**Dose Modifications (cisplatin, doxorubicin, methotrexate, vinblastine)**
1 or greater	100%
less than 1	1st Occurrence. Delay until recovery. If this occurs within seven days resume treatment at the last dose administered. If this takes longer than seven days then give 75% of the last dose 2nd Occurrence Delay until recovery then give 75% of the last dose
Platelets ($x10^9$/L)	**Dose Modifications (cisplatin, doxorubicin, methotrexate, vinblastine)**
100 or greater	100%
Less than 100	1st Occurrence. Delay until recovery. If this occurs within seven days resume treatment at the last dose administered. If this takes longer than seven days then give 75% of the last dose 2nd Occurrence Delay until recovery then give 75% of the last dose

Hepatic Impairment

Drug	Bilirubin µmol/L	Dose (% of original dose)	AST/ALT units/L
Cisplatin	N/A	No dose adjustment needed	N/A
Doxorubicin	20-51	50%	If the AST 2-3xULN then give 75% of the dose If the AST is greater than 3xULN then give 50% of the dose
	52-85	25%	
	80 or greater	omit	
Methotrexate	less than 50	100	If the AST is greater than 180 administer 75% of the dose
	51-85	75	
	86 or greater	omit	
Vinblastine	26-51	50	*If the AST is greater than 180 and bilirubin less than 52 administer 50% of the dose *If the AST is greater than 180 and the bilirubin 52 or greater omit vinblastine
	52 or greater	50 or omit*	

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin	60 or more	100%
	less than 60	consider alternative
Doxorubicin	No dose reduction necessary	
Methotrexate	46-60	65
	31-45	50
	less than 30	omit
Vinblastine	No dose reduction necessary	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 75% of the original dose or discontinued as appropriate.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops.

Regimen

14 day cycle for 6 cycles

Drug	Dose	Days	Administration
Cisplatin	70mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a rate of cisplatin of 1mg/min (minimum 120 minutes)
Doxorubicin	30mg/m^2	1	Intravenous bolus over 10 minutes
Methotrexate	30mg/m^2	1	Intravenous bolus over 10 minutes
Vinblastine	3mg/m^2	1	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

Dose Information

- Cisplatin will be dose banded according to the CSCCN agreed bands
- Doxorubicin will be dose banded according to the CSCCN agreed bands
- Methotrexate will be dose banded according to the CSCCN agreed bands
- Vinblastine will be rounded to the nearest 1mg (up if halfway)

Administration Information

Extravasation

- Cisplatin - exfoliant
- Doxorubicin - vesicant
- Methotrexate - inflammitant
- Vinblastine - vesicant

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - aprepitant 125mg oral
  - dexamethasone 4mg oral or intravenous
  - ondansetron 8mg oral or intravenous

As take home medication

- aprepitant 80mg oral daily for on days 2 and 3
- dexamethasone 4mg oral once a day for 3 days
- metoclopramide 10mg oral three times a day as required
- ondansetron 8mg oral twice a day for 3 days

- Cisplatin pre and post hydration as follows

  Pre

  Furosemide 40mg oral or intravenous

  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Post

  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.

- Growth factors according to local formulary;
  - filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 3 subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 3 subcutaneous
  - pegfilgrastim or bioequivalent 6mg once only on day 2 subcutaneous

- Mouthwashes according to local or national policy on the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

Coding (OPCS 4.6)

- Procurement – X70.4

- Delivery – X72.1

References
1. Edeline et al. Accelerated MVAC chemotherapy in patients with advanced bladders cancer previously treated with a platinum-gemcitabine regimen. Eur Journal of Cancer (2012); 48: 1141-1146.
2. Sternberg CN, de Mulder PH, Schornagel JH et al. Randomised phase III trial of high dose intensity methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony stimulating factor versus classic MVAC in advanced urothelial tract tumours: European Organization for Research and Treatment of Cancer Protocol No 30924. J Clin Oncol 2001; 19 (10): 2638-2646.

REGIMEN SUMMARY

Cisplatin-Doxorubicin-Methotrexate-Vinblastine (AccMVAC)

Day 1

1. Aprepitant 125mg oral
2. Dexamethasone 4mg oral or intravenous
3. Ondansetron 8mg oral or intravenous
4. Doxorubicin 30mg/m^2 intravenous bolus over 10minutes
5. Vinblastine 3mg/m^2 intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
6. Methotrexate 30mg/m^2 intravenous bolus over 10 minutes
7. Furosemide 40mg oral or intravenous
8. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes
9. Cisplatin 70mg/m^2 in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion at a rate of cisplatin of 1mg/min (minimum 120 minutes)
10. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol with potassium chloride 20mmol intravenous infusion over 60 minutes

Take Home Medicines

11. Aprepitant 80mg once a day on days 2 and 3 oral
12. Dexamethasone 4mg once a day for 3 days oral starting the day after chemotherapy
13. Metoclopramide 10mg three times a day when required for nausea oral
14. Ondansetron 8mg twice a day for 3 days oral starting on the evening of treatment
15. Growth factors according to local formulary

    Administration Instructions
    - filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 3 subcutaneous
    - lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 3 subcutaneous
    - pegfilgrastim or bioequivalent 6mg once only on day 2 subcutaneous

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	May 2015	Header changed Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Tables reformatted. Vinblastine added to renal table. Vinblastine dose modifications in hepatic impairment updated. Mucositis recommendation changed Growth factors updated with new units OPCS code updated Dexamethasone TTO clarified Ondansetron TTO clarified Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	Dec 2012	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr J Gale Consultant Medical Oncologist Dr M Wheater Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.