M-VAC: Methotrexate / Vinblastine / Doxorubicin / Cisplatin for Bladder Cancer

Indication:
1) Neoadjuvant therapy for transitional cell carcinoma of the bladder
2) Palliative alternative therapy to Gemcitabine / Cisplatin in Advanced or Metastatic Bladder Cancer

Regimen details:
- Methotrexate 30mg/m² IV D1, D15, D22
- Vinblastine 3mg/m² IV D2, D15, D22
- Doxorubicin 30mg/m² IV D2
- Cisplatin 70mg/m² IV D2
- Pegfilgrastim 6mg SC D3

Administration:

Day 1  Methotrexate, IV bolus injection via a fast-running Sodium Chloride 0.9% infusion

Day 2  Doxorubicin, IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion over 3 – 10 minutes
- Vinblastine in 50 mls Sodium Chloride 0.9% IV infusion over 5 – 10 minutes
- Furosemide 40mg orally
- 1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV infusion over 60 minutes
- Cisplatin, in 1 litre Sodium Chloride 0.9% IV over 2 hours
- 1 litre Sodium Chloride 0.9% + 40mmol KCl + 1g MgSO₄ IV infusion over 2 hours
- Then either 500ml Sodium Chloride 0.9% IV infusion over 60 minutes or 500ml drinking water
- Any device containing aluminium that may come in contact with Cisplatin must be avoided
- *Follow local guidance on Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens

Day 3  Pegfilgrastim 6mg subcutaneously

Day 15  Vinblastine in 50 mls Sodium Chloride 0.9% IV infusion over 5 – 10 minutes
- Methotrexate, IV bolus injection via a fast-running Sodium Chloride 0.9% infusion

Day 22  Vinblastine in 50 mls Sodium Chloride 0.9% IV infusion over 5 – 10 minutes
- Methotrexate, IV bolus injection via a fast-running Sodium Chloride 0.9% infusion

Frequency:
- Every 28 days, for 3 cycles (Neoadjuvant setting)
- Every 28 days, for 6 cycles (Palliative setting)

Extravasation:
- Doxorubicin and Vinblastine : Vesicants
- Cisplatin and Methotrexate : Non-vesicants

Anti- emetics:
- Days 1 : Minimal emetogenic
- Day 2 : Highly emetogenic
- Days 15 and 22 : Low emetogenic
- Follow Local Anti-emetic Policy

Reason for Update: Network Protocol Development
Version: 1
Approved by Urology Consultant: Hartmut Kristeleit
Supersedes: All other versions
Date: 07.01.10
 Prepared by: Maria Teresa Pacheca-Palomar Dec’09
Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley
Date: 29/01/2010
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Supportive medication: Mouthwashes (as per local policy) for mucositis
Loperamide 4mg po stat then 2mg prn for diarrhoea

Regular investigations:
- FBC D1, D15, D22
- LFTs D1
- U&Es D1
- Mg^{2+} and Ca^{2+} D1
- EDTA Prior to 1st cycle (see Renal impairment)
- MUGA scan/Echocardiogram Prior to 1st cycle (see Comments)
- Clinical toxicity assessment Every cycle

Comments:
Ascites&pleural effusions – Methotrexate toxicity
If the patient has a “third –space” fluid collection (ascites, effusion or extensive oedema) or significant renal impairment or toxicities such as mucositis, sore eyes or diarrhoea, the elimination of Methotrexate may be prolonged, enhancing its toxicity. Seek Consultant advice and consider folinic acid rescue in such cases (ensure this is charted to start 24 hours after Methotrexate)

Interstitial pneumonitis - Methotrexate
Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur with methotrexate and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit.

Hydration - Cisplatin
Encourage oral hydration during treatment; for instance, drink a glass of water every hour during treatment, and at least a further 2 litres over the 24 hours following treatment. 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. For low urine output, consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 kg, or symptoms of fluid overload.

Allergy – Cisplatin
Anaphylactic-like reactions to Cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of Cisplatin administration. Adrenaline, corticosteroids and antihistamines have been effectively employed to alleviate symptoms. No further Cisplatin should be given without Consultant approval.

Electrolyte disturbances – Cisplatin
Disturbances in electrolytes can be a long term manifestation due to the Cisplatin induced renal tubular dysfunction. Check electrolytes- additional supplementation of magnesium, calcium or potassium may be required.
Maximum cumulative dose Doxorubicin = 450 - 550mg/m²
A baseline MUGA scan or Echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, diabetes, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan or Echocardiogram should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum.

**DOSE MODIFICATIONS**

**Haematological Toxicity**

**Neoadjuvant and Palliative setting:**

- WBC < 3.0 x 10⁹/l
  - Delay for 1 week. Consider a longer course of G-CSF if appropriate.
- Neutrophils < 1.0 x 10⁹/l
  - Repeat FBC - If within normal parameters, resume treatment at 100% doses
- Platelets < 100 x 10⁹/l
  - If febrile neutropenia or poor performance status, discuss with Consultant

**D15 and D22**

In the Neoadjuvant and Palliative setting, treatment on Days 15 and 22 should not be delayed if the blood count is too low – it should be omitted altogether. The aim is to give Day 1 treatment every 28 days, even if Day 15 and/or Day 22 drugs have been omitted:

- WBC < 2.0 x 10⁹/L
  - Omit therapy
- Platelets < 75 x 10⁹/L

**Renal Impairment:**

GFR should be calculated using the Cockcroft & Gault equation in all patients; if the calculated GFR < 60 or > 120ml/min, measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if >25% from baseline value, re-calculate GFR using the Cockcroft & Gault equation.

**Vinblastine:** No dose reduction necessary

**Doxorubicin:** Dose reduction in severe renal impairment (GFR < 10 ml/min) should be discussed with the Consultant

**Methotrexate:** Use with extreme caution in patients with renal impairment

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Methotrexate Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>Give 100%</td>
</tr>
<tr>
<td>60 – 80</td>
<td>Give 65%</td>
</tr>
<tr>
<td>30 – 59</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

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Cisplatin induces nephrotoxicity, which is cumulative. Cisplatin dose should be reduced as follows:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
</tr>
<tr>
<td>51 - 60</td>
<td>Give 75%</td>
</tr>
<tr>
<td>40 - 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

**Hepatic Impairment:** Cisplatin: No dose reduction necessary

Methotrexate is contraindicated in impaired hepatic function. Hepatotoxicity, including hepatitis and cirrhosis, has been associated with Methotrexate. It is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy.

<table>
<thead>
<tr>
<th>Bilirubin (µmol/l)</th>
<th>AST (µmol/l)</th>
<th>Methotrexate Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 52, and</td>
<td>&lt; 180</td>
<td>Give 100%</td>
</tr>
<tr>
<td>53 – 84, or</td>
<td>&gt; 180</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>-</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Vinblastine: It is excreted principally by the liver, it may be necessary to reduce Vinblastine dose in the presence of significantly impaired hepatic or biliary function.

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT (units)</th>
<th>Vinblastine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 – 51 or 60 – 180</td>
<td>Normal</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&gt; 51 and Normal</td>
<td>&gt; 180</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&gt; 51 and &gt; 180</td>
<td></td>
<td>Omit</td>
</tr>
</tbody>
</table>

Doxorubicin dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Doxorubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>51 – 85</td>
<td>Give 25%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>Omit</td>
</tr>
</tbody>
</table>

**Toxicities:** Myelosuppression; nausea; vomiting; mucositis; diarrhoea; constipation; nephrotoxicity; neurotoxicity / ototoxicity; cardiotoxicity; electrolyte disturbances; anaphylactic – like reactions; alopecia; interstitial pneumonitis (rare)
Drug interactions:  

Methotrexate, Vinblastine, Doxorubicin and Cisplatin:
- Clozapine: increased risk of agranulocytosis, avoid concomitant use
- Digoxin tablets: reduced absorption (resolved by giving the digoxin in liquid)
- Phenytoin: reduced absorption of the antiepileptic

Methotrexate
- Antibacterials: Penicillins, doxycycline, tetracyclines, sulphonamides and ciprofloxacin may reduce Methotrexate clearance. Monitor FBC
- Co-trimoxazole/Trimethoprim: increases antifolate effect. Avoid if possible. If must be used, monitor FBC
- NSAIDs: may reduce renal excretion of Methotrexate (increased risk in those with renal impairment). Monitor renal function and FBC if used concomitantly
- Probenecid: increases Methotrexate toxicity. Avoid

Vinblastine
- Cisplatin: cause higher plasma concentration of Vinblastine
- Erythromycin: may increase the toxicity of Vinblastine, avoid concomitant use
- Itraconazole and Posaconazole: increased risk of neurotoxicity
- Mitomycin C: acute respiratory distress and pulmonary infiltration

Doxorubicin
- Ciclosporin (high dose) increase Doxorubicin serum levels and myelotoxicity
- Concomitant use of other cardioactive compounds e.g. calcium channel blockers require monitoring of cardiac function throughout treatment
- Quinolones: antimicrobial effect of quinolones decreased
- Warfarin: the anticoagulant effect is increased

Cisplatin
- Allopurinol, colchicine, probenecid, sulfipyrazone: increase in serum uric acid concentration
- Cephalosporins, aminoglycosides, amphotericin B: increase nephrotoxic and ototoxic effects of Cisplatin in these organs
- Ciclosporin: excessive immunosuppression, with risk of lymphoproliferation
- Cyclizine, phenothiazines: may mask ototoxicity symptoms
- Furosemide, hydralazine, diazoxide and propranolol: intensify nephrotoxicity
- Oral anticoagulants: require an increased frequency of the INR monitoring
- Methotrexate: increased pulmonary toxicity
- Penicillamine: may diminish the effectiveness of Cisplatin
- Phenytoin: reduced epilepsy control

References:

www.medicines.org.uk
South East London Cancer Network

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SWSHCN- Approved Network Regimen for Bladder Cancer. Accelerated MVAC. December 2007
CCO Formulary. M-VAC. Revised November 2004
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
NLCN- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
NLCN- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
CTCAE v3.0. August 2006