MMM : Mitomycin C / Methotrexate / Mitoxantrone in Advanced Breast Cancer

Indication: Fourth line palliative therapy for Advanced Breast Cancer, especially appropriate to be used in a situation where a standard regimen is deemed inadequate for specific clinical reasons

Regimen details: Mitomycin C 7mg/m² IV D1
Methotrexate 30mg/m² IV D1 and D21
Mitoxantrone 7mg/m² IV D1 and D21

Administration: Mitomycin C, by slow IV injection into the side-arm of a free-running Sodium Chloride 0.9% drip
Mitoxantrone, by slow IV injection into the side-arm of a free-running Sodium Chloride 0.9% drip
Methotrexate is given by slow IV push into the side arm of a fast flowing drip of Sodium Chloride 0.9%

Frequency: Every 42 days, for 3 cycles

Extravasation: Mitomycin C : Vesicant
Methotrexate and Mitoxantrone are non-vesicants

Anti- emetics: Moderate emetogenic
Follow local Anti-emetic policy

Supportive medication: Mouthwashes (as per local policy) for mucositis
Folinic acid rescue 15mg po 6 hourly x 6 doses, starting 24 hours post Methotrexate (only required for patients with toxicities such as mucositis, sore eyes, diarrhoea or severe renal impairment or “third –space” fluid collection).See Comments below

Regular investigations: FBC Baseline & pre D1
LFTs Baseline & pre D1
U&Es Baseline & pre D1
CT scan Every 3 cycles
MUGA scan Prior to 1st cycle (for patients with cardiac risk factors)

Comments : Folinic acid rescue – Methotrexate
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 (make sure it is charted to start 24 hours after Methotrexate)

Interstitial pneumonitis – Methotrexate
Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur 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
Haemolytic-uremic syndrome – Mitomycin C
A syndrome of renal failure and microangiopathic haemolytic anaemia with hypertension and neurological symptoms (haemolytic-uremic syndrome) has been reported in 10% patients. This syndrome usually appears after 6 months of therapy of Mitomycin C, and may be exacerbated with blood transfusions. Patients should be monitored for development of renal failure or haemolysis.

Cardiotoxicity – Mitoxantrone
Cardiac events, including congestive heart failure and decreases in left ventricular ejection fraction have been reported during Mitoxantrone therapy. Cardiac monitoring should be performed in patients with pre-existing heart disease or who have had prior treatment with anthracyclines or prior mediastinal/thoracic radiotherapy. Cardiotoxicity also seems to be more likely to occur at Mitoxantrone cumulative doses in excess of 160mg/m², or 100mg/m² after previous anthracycline therapy.

DOSE MODIFICATIONS

**Haematological Toxicity**

**D1**

WBC < 3.0 x 10⁹/L

or

Neutrophils < 1.5 x 10⁹/L

or

Platelets < 100 x 10⁹/L

Delay for 1 week.

Repeat FBC - If within normal parameters, resume treatment at full dose

Doses are reduced to 75% after 2 dose delays or an incident of Neutropenic infection, and to 50% after 4 dose delays

**Renal Impairment**

**Mitomycin C**: Renal function should be monitored before each cycle

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Mitomycin C Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Give 75%</td>
</tr>
</tbody>
</table>

**Mitoxantrone**: No dose reductions necessary

**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>
Hepatic Impairment

Mitomycin C: Dose reduction probably not necessary. Discuss appropriate dose with Consultant when AST levels > 2 x ULN

Mitoxantrone: Careful supervision is recommended when treating patients with severe hepatic insufficiency. Clinical decision depends on bilirubin level and performance status

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Performance status</th>
<th>Mitoxantrone Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 59</td>
<td>Good</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>Good</td>
<td>60%</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>Poor</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

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>

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

Toxicities: Myelosuppression; nausea; vomiting; mucositis; diarrhoea; interstitial pneumonitis; cardiotoxicity; haemolytic-uremic syndrome (rare); rash; discoloured (blue-green) urine

Drug interactions: Mitomycin C
- Tamoxifen: increased risk of haemolytic-uraemic syndrome

Methotrexate
- Antibacterial drugs e.g. penicillin, doxycycline, tetracycline, sulphonamides, ciprofloxacin etc., may reduce Methotrexate clearance. Monitor FBC
- Clozapine: increased risk of agranulocytosis; avoid concomitant use
- Hepatotoxic drugs, including alcohol, should be avoided
- NSAIDs: may reduce Methotrexate renal excretion. Monitor renal function & FBC
- Phenytoin: reduced absorption of the antiepileptic
- Probenecid: may reduce Methotrexate excretion; increased risk of toxicity
- Retinoids: increased risk of hepatotoxicity. Avoid concomitant use
- Trimethoprim/Co-trimoxazole: increased antifolate effect, can cause acute megaloblastic pancytopenia. Avoid if possible

Mitoxantrone
- Cardiotoxic drugs increase the risk of cardiac toxicity

Reason for Update: Network Protocol Development
Version: 1
Supersedes: All other versions
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Approved by SELCN DTAC Chair: Nic Ketley

Approved by Breast Consultant: Bruce Bryant
Date: 05.12.08
Checked by (Network Pharmacist): Jacky Turner
Date: 10.02.09
References:

www.medicines.org.uk
Summary of Product Characteristics. Mitomycin C. Kyowa Hakko UK Ltd. Dec’07
CCO Formulary. MMM. Revised March 2004
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
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GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
CTCAE v3.0. August 2006