MVP: Mitomycin C / Vinblastine / Cisplatin in Advanced Breast Cancer

Indication: Fourth line palliative therapy in patients with Metastatic Breast Cancer previously treated with anthracyclines or taxanes

Regimen details: Mitomycin C 8mg/m² (max. 14mg) IV D1 (on cycles 1, 2, 4 and 6 only)
Vinblastine 6mg/m² (max. 10mg) IV D1
Cisplatin 50mg/m² IV D1

Administration: Furosemide 40mg orally
1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV infusion over 60 minutes
Mitomycin C, IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion
Vinblastine in 50 mls Sodium Chloride 0.9% IV infusion over 5 – 10 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
*Follow guidance protocol for Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens
Any device containing aluminium that may come in contact with Cisplatin must be avoided

Frequency: Every 21 days, for 6 cycles

Extravasation: Mitomycin C and Vinblastine are vesicants
Cisplatin: Non-vesicant

Anti-emetics: Moderate emetogenic
Follow Local Anti-emetic Policy

Regular investigations:
FBC D1
LFTs D1
U&E s D1
Mg²⁺ and Ca²⁺ D1
EDTA Prior to 1ˢᵗ cycle
CT scan Every 3 cycles

Comments: 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
Pulmonary toxicity – Mitomycin C
Pulmonary toxicity typically presents as dyspnoea and non-productive cough. Administration of vinca alkaloids to patients who have previously or simultaneously received Mitomycin C may cause severe or life-threatening dyspnoea and bronchospasm within minutes to hours. Bronchodilators, steroids and/or oxygen have produced symptomatic relief

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

DOSE MODIFICATIONS

Haematological Toxicity

Day1

<table>
<thead>
<tr>
<th>WBC &lt; 3.0 x 10^9/l</th>
<th>Delay for 1 week.</th>
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<tbody>
<tr>
<td>or</td>
<td>Repeat FBC - If within normal parameters, resume treatment and discuss possible dose reduction with Consultant</td>
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<tr>
<td>Neutrophils &lt; 1.5 x 10^9/l</td>
<td></td>
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<tr>
<td>or</td>
<td></td>
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<tr>
<td>Platelets &lt; 100 x 10^9/l</td>
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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
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>
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</tbody>
</table>

Mitomycin C

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

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Cisplatin Dose</th>
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<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 Consider Carboplatin AUC 5</td>
</tr>
</tbody>
</table>

Cisplatin

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

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</td>
<td>or 60 – 180</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>and Normal</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>and &gt; 180</td>
<td>Omit</td>
</tr>
</tbody>
</table>

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS AppROPRIATE

NEUROPATHY/ OTOTOXICITY – CISPLATIN

If patient develops symptoms indicative of Grade 2 Neuropathy (paresthesia interfering with function, but not interfering with activities of daily living) or Ototoxicity (tinnitus not interfering with activities of daily living), seek Consultant advice and consider changing Cisplatin to Carboplatin

Toxicities: Myelosuppression; nausea; vomiting; anorexia; diarrhoea; peripheral neuropathy; alopecia (reversible); hearing impairment; nephrotoxicity (cumulative); renal failure and microangiopathic haemolytic anaemia (haemolytic-uremic syndrome); pulmonary toxicity; infertility
Drug interactions:

Mitomycin C
- Clozapine : increased risk of agranulocytosis, avoid concomitant use
- Tamoxifen : haemolytic anaemia, thrombocytopenia, renal impairment
- Vinca alkaloids : shortness of breath and bronchospasm
Bronchodilators, steroids and/or oxygen have produced symptomatic relief

Vinblastine
- Anticonvulsants : serum levels of anticonvulsants may be reduced by Vinblastine
- Cisplatin : cause higher plasma concentration of Vinblastine
- Clozapine : increased risk of agranulocytosis, avoid concomitant use
- Erythromycin : may increase the toxicity of Vinblastine, avoid concomitant use
- Itraconazole : increased risk of neurotoxicity
- Mitomycin C : acute respiratory distress and pulmonary infiltration

Cisplatin
- Allopurinol, colchicine, probenecid, sulfinpyrazone : 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
- Penicillamine : may diminish the effectiveness of Cisplatin
- Phenytoin : reduced epilepsy control

References:

www.medicines.org.uk
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
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