Breast Pathway Group – Oral Cyclophosphamide & Methotrexate in Advanced Breast Cancer

Indication: Pretreated metastatic breast cancer with ECOG performance status 0 - 2
Previously untreated metastatic breast cancer in patients unsuitable for other chemotherapy drugs due to excess toxicity risk

Regimen details:
- Cyclophosphamide 50mg ONCE a day PO Continuous therapy
- Methotrexate 2.5mg TWICE a day PO Day 1 & 2 each WEEK

Administration: Orally, tablets to be swallowed whole, do not chew or crush.
Take with a full glass of water.
Cyclophosphamide available as 50mg tablets
Methotrexate available as 2.5mg tablets

Frequency: Prescribed every 28 days - continue treatment according to response or unacceptable toxicity occurs

Pre-medication: Not routinely required

Anti-emetics: Low emetogenicity
Follow Local Anti-emetic Policy

Supportive medication: Mouthcare as per local policy

Regular investigations:
- Prior to cycle 1
  - FBC Day 1 (within 14 days)
  - LFTs Day 1 (within 14 days)
  - U&Es Day 1 (within 14 days)
  - CXR Baseline, then as clinically indicated
Prior to Day 1 (all cycles)

- FBC: Every 2 weeks until stabilised, then Day 1 (within 72 hours)
- LFTs: Day 1 (within 72 hours)
- U&Es: Day 1 (within 72 hours)

Toxicities:
Myelosuppression, nausea, vomiting, anorexia, diarrhoea, skin reactions (rash, dry skin, pruritis, blisters, pigmentation), nail changes, alopecia, mucositis, taste change, anaemia, interstitial pneumonitis, elevation of liver enzymes and liver toxicity, renal toxicity, haematuria/haemorrhagic cystitis, blurred vision, azospermia, secretion of anti-diuretic hormone (fluid retention and hyponatremia)

**DOSE MODIFICATIONS**

**Haematological Toxicity**

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 &amp; ≥ 100</td>
<td></td>
<td>100% dose</td>
</tr>
<tr>
<td>1.0 – 1.49 &amp; / or 75 - 99</td>
<td></td>
<td>Proceed at 50% dose reduction for both drugs</td>
</tr>
<tr>
<td>&lt; 1.0 &amp; / or &lt; 75</td>
<td></td>
<td>Delay 1 week. Repeat FBC, if recovered then restart treatment with 50% dose reduction for both drugs</td>
</tr>
</tbody>
</table>

**Non-haematological Toxicities**

**Renal Impairment**

**Methotrexate**

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Methotrexate Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>100% dose</td>
</tr>
<tr>
<td>10 – 50</td>
<td>2.5mg ONCE a day on Day 1 &amp; 2 each week</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Contra-indicated</td>
</tr>
</tbody>
</table>

**Cyclophosphamide**
Renal failure may lead to reduced excretion of metabolites and increased toxicity. Severe renally impaired patients (CrCl <10 ml/min) are at particular risk, consider 50% dose reduction

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Hepatic Impairment

Methotrexate

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST / ALT (Units)</th>
<th>Methotrexate Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>&amp;</td>
<td>100% dose</td>
</tr>
<tr>
<td>51 - 85</td>
<td>or</td>
<td>2.5mg ONCE a day on Day 1 &amp; 2 each week</td>
</tr>
<tr>
<td>&gt; 85</td>
<td></td>
<td>Contra-indicated</td>
</tr>
</tbody>
</table>

Cyclophosphamide

Consider dose reduction if transaminases or ALP > 2-3 x ULN. Clinical decision.

Dose modifications for other toxicities as appropriate

Withhold treatment for ≥ grade 2 non-haematological toxicity: anorexia, nausea, vomiting, diarrhoea, stomatitis, dry mouth, increased transaminases, epigastric pain, until resolved then consider dose reducing by 50%.

Location of regimen delivery:

Outpatient setting

Comments:

Patients able to tolerate oral dosage forms
To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan.

Drug interactions:

Avoid use of live vaccines – increased risk of infection

Methotrexate

Drugs with antifolate properties (e.g. co-trimoxazole, trimethoprim) – increased methotrexate toxicity
Aspirin / NSAIDS- reduced excretion of methotrexate, increased risk of toxicity
Phenytoin – reduced phenytoin effectiveness, increase risk of methotrexate toxicity
Warfarin – increases INR, risk of bleeding
Clozapine - increased risk of agranulocytosis, avoid concomitant use
Probencid - increased effect of methotrexate
Retinoids – increases methotrexate levels, increase risk of hepatotoxicity
Vitamin products containing folic acid may alter response
Increased risk of toxicity with haematotoxic/hepatotoxic drugs (eg. Leflunomide)

Cyclophosphamide

Effect of oral hypoglycaemic agents may be potentiated
Allopurinol: can increase the incidence of serious bone marrow depression
Amiodarone: increased risk of pulmonary fibrosis; avoid combination if possible
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Avoid grapefruit juice for 48 hours before and on day of cyclophosphamide
Indapamide: prolonged leucopenia is possible
Itraconazole: might increase Cyclophosphamide side effects e.g. haemorrhagic cystitis, pigmentation of palms, nails and soles etc.
Warfarin: anticoagulant effect is increased

References:
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009
LCA Breast Cancer Clinical Guidelines October 2013