Nordic Protocol (Maxi-CHOP and High Dose Cytarabine) for Mantle Cell Lymphoma (MCL)

Indication: Mantle Cell Lymphoma, Stage II to IV, < 60-65 years, good performance status.

Rituximab for this protocol is funded via the CDF.

Regimen details: Cycle 1: Maxi-CHOP 21 (No Rituximab in cycle 1)
- Cyclophosphamide 1200mg/m² IV Day 1
- Doxorubicin 75mg/m² IV Day 1
- Vincristine 2mg IV Day 1
- Prednisolone 100mg Orally Days 1 to 5

Cycles 2 and 4: R-High Dose Cytarabine
- Rituximab 375mg/m² IV Day 1
- Cytarabine 3000mg/m² BD IV Days 1 and 2

Cycles 3 and 5: R-Maxi-CHOP 21
- Rituximab 375mg/m² IV Day 1
- Cyclophosphamide 1200mg/m² IV Day 1
- Doxorubicin 75mg/m² IV Day 1
- Vincristine 2mg IV Day 1
- Prednisolone 100mg Orally Days 1 to 5

Cycle 6: R-High Dose Cytarabine + R Stem Cell Mobilisation
- Rituximab 375mg/m² IV Days 1 and 9
- Cytarabine 3000mg/m² BD IV Days 1 and 2
- GCSF as per Stem Cell Transplant Team for this cycle.

Administration:
- Rituximab IV infusion in 500ml sodium chloride 0.9%. Rate as per rituximab administration guidance.
- Cyclophosphamide IV infusion in 100-250ml sodium chloride 0.9% over 30 minutes or as an IV bolus
- Doxorubicin Slow IV bolus into the side arm of a free-running drip of sodium chloride 0.9%
- Vincristine IV infusion in 50ml sodium chloride 0.9% over 5 minutes.
- Prednisolone Orally, with or after food. Available as 5mg and 25mg tablets.
- Cytarabine IV infusion in 1000ml sodium chloride 0.9% over 3 hours.

Premedication:
- 30 minutes prior to rituximab:
  - Paracetamol 1000mg orally
  - Chlorphenamine 10mg IV
  - Prednisolone 100mg orally (Day 1 of Maxi-CHOP chemotherapy) OR
  - Hydrocortisone 100mg IV

Frequency: Every 21 days (3 cycles of each regimen, alternating)
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Extravasation: Vincristine and doxorubicin are vesicants and should be administered with appropriate precautions to prevent extravasation. If there is any possibility that extravasation has occurred, contact a senior member of the medical team and follow local protocol for dealing with cytotoxic extravasation. Cyclophosphamide, cytarabine and rituximab are not vesicants.

Anti-emetics: High emetogenic potential (60% - 90%) incidence. Follow local anti-emetic policy.

Supportive medication: Allopurinol 300mg od orally (100mg if renal impairment) for prevention of tumour lysis syndrome for first cycle only. PPI prophylaxis e.g. omeprazole 20mg od orally. For Maxi-CHOP cycles: Mesna 800mg 2 hours pre-CHOP and 2 and 6 hours post-CHOP. For High Dose Cytarabine cycles: Corticosteroid eye drops as per local formulary (e.g. prednisolone (Predsol®) 0.5% or dexamethasone (Maxidex®) 0.1%), during and for 3 days after completion of chemotherapy. GCSF: preparation as per local policy. For primary prophylaxis of febrile neutropenia as per local policy.

Regular investigations: Baseline & regular
- FBC Prior to each cycle
- LFTs Prior to each cycle
- U&Es Prior to each cycle

Dose Modifications

Haematological Toxicity

Cycle 1 will go ahead full dose even if FBC is not normal.

<table>
<thead>
<tr>
<th>Neutrophils (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5 x 10⁹/L &amp; ≥ 100 x 10⁹/L</td>
<td>100% dose</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 x 10⁹/L or &lt; 100 x 10⁹/L</td>
<td>Delay until neutrophils &gt; 1.5 x 10⁹/L and platelets &gt; 100 x 10⁹/L</td>
<td></td>
</tr>
</tbody>
</table>

Renal Impairment

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cyclophosphamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20</td>
<td>Give 100%</td>
</tr>
<tr>
<td>10 – 20</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

High dose cytarabine: consider dose reduction if CrCl < 60ml/min. Doxorubicin and vincristine: no dose reductions required.

Confirm any dose reductions with the Consultant, because in some circumstances 100% dose may be appropriate.
Hepatic Impairment

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

<table>
<thead>
<tr>
<th>Bilirubin (µmol/l)</th>
<th>Vincristine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 51</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 51 - 85</td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>Omit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bilirubin (µmol/l)</th>
<th>Cytarabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 34</td>
<td>100% dose</td>
</tr>
<tr>
<td>&gt; 34</td>
<td>50% dose</td>
</tr>
</tbody>
</table>

Confirm any dose reductions with the Consultant, because in some circumstances 100% dose may be appropriate.

Toxicities: Myelosuppression, cardiotoxicity
Neurotoxicity – monitor for constipation or peripheral sensory loss and discuss with Consultant before administering further cycles. Consider dose reducing vincristine to 1mg or substituting for vinblastine.
Cytarabine: ocular pain, foreign body sensation, photophobia and blurred vision.
Dizziness, headache, confusion, cerebellar toxicity. Skin freckling, itching, at injection site, rash, skin sloughing of the palmar and plantar surfaces. Myalgia and bone pain

Drug interactions: Concurrent administration of vincristine and itraconazole, voriconazole, posaconazole have been reported to cause increased severity of neuromuscular side effects and are therefore contra-indicated.

Comments: Maximum cumulative lifetime dose doxorubicin = 450 - 550mg/m²
A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum.