R-Hyper-CVAD / R-MA

INDICATION

Aggressive lymphomas, including acute lymphoblastic leukaemia / lymphoma.

Omit rituximab if CD20-negative.
Consider omitting intrathecals if treating mantle cell lymphoma.

TREATMENT INTENT

Curative or Disease modification (depending on disease type).

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis) or PET/CT, presence or absence of B symptoms, clinical extent of disease. Consider bone marrow aspirate and trephine if clinically indicated.
3. Blood tests - FBC, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β₂ microglobulin, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
4. A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.
5. Patients MUST NOT receive co-trimoxazole, starting from the week before the first methotrexate infusion. Consider pentamidine treatment if considered at risk from Pneumocystis infection.
6. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of childbearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
7. ECG +/- Echo - if clinically indicated.
8. Record performance status, height and weight.
9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
10. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Hydration - in patients with bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol.
12. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. Arrange insertion of double-lumen central venous catheter.
14. Treatment should be agreed in the relevant MDT.
DRUG REGIMEN

R-Hyper-CVAD - Cycles 1, 3, 5, 7:

Day 0  METHOTREXATE  12 mg INTRATHECAL.
Day 1  Pre-med with Chlorphenamine 10 mg IV, paracetamol 1 g 30 minutes before rituximab. Give day 1 dexamethasone at least 30 minutes prior to rituximab.
RITUXIMAB 375 mg/m² IV infusion daily in 500 mL sodium chloride 0.9%.
Days 1 to 3  MESNA 600 mg/m² per day IV continuous infusion in 1000 mL sodium chloride 0.9% over 24 hours (to begin 1 hour before cyclophosphamide and stopping 12 hours after final dose).
Days 1 to 3  CYCLOPHOSPHAMIDE 300 mg/m² twice a day IV infusion in 250 mL sodium chloride 0.9% over 2 hours for 6 doses.
Days 1 to 4  DEXAMETHASONE 40 mg PO/IV daily (2 mg tablets).
Day 4  DOXORUBICIN 50 mg/m² IV infusion daily in 100 mL sodium chloride 0.9% over 2 hours.
Day 4  VINCIRISTINE 1.4 mg/m² (maximum 2 mg) IV infusion in 50 mL sodium chloride 0.9% over 10 minutes. Consider capping at 1 mg in the over 70 year old age group.
Day 5  G-CSF as per local policy. Continue until neutrophils >1.0 x 10⁹/L for 3 consecutive days.
Day 7  CYTARABINE 100 mg INTRATHECAL.
Days 8 to 11  DEXAMETHASONE 40 mg PO/IV daily (2 mg tablets).
Day 11  VINCIRISTINE 1.4 mg/m² (maximum 2 mg) IV infusion in 50 mL sodium chloride 0.9% over 10 minutes. Consider capping at 1 mg in the over 70 year old age group.

R-MA - Cycles 2, 4, 6, 8:

Day 0  Hydration / Alkalisation - Pre methotrexate (starting T= -12 hours). Refer to sections below.
Day 1  RITUXIMAB 375 mg/m² IV infusion daily in 500 mL sodium chloride 0.9%.
Day 1 (T=0)  METHOTREXATE  1 g/m² IV infusion [start at 10.00 hrs] Day 1 in exactly 500 mL sodium chloride 0.9% over 24 hrs.
Calcium folinate (Folinic acid) post methotrexate (starting 36 hours from the start of methotrexate). Refer to sections below.
Day 2  METHOTREXATE 12 mg INTRATHECAL (following completion of IV methotrexate).
Days 3 & 4  CYTARABINE* 3 g/m² IV infusion (at 24, 36, 48 and 60 hours after completion of IV methotrexate) in 500 mL sodium chloride 0.9% over 2 hours.
Day 5  G-CSF as per local policy. Continue until neutrophils >1.0 x 10⁹/L for 3 consecutive days.
Day 7  CYTARABINE 100 mg INTRATHECAL.
NB: * Patients aged 60 years or more, reduce cytarabine to 1 g/m².
INTRAVENTOUS HYDRATION

Start: T = -12 hours.
Fluid: 1000 mL glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 100 mmol added. Following completion of methotrexate infusion, decrease amount of sodium bicarbonate in fluids to 50 mmol/L.
Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m²).
Duration: Continue fluids during methotrexate infusion (run concurrently with methotrexate, through one arm of Y extension). Administer fluids until methotrexate level <0.1 micromol/L.

METHOTREXATE INTRAVENTOUS INFUSION

Start: T = 0 (aim to start at 10.00 am)
Levels: Check 48 hours after the start of the methotrexate infusion, and every 24 hours thereafter until methotrexate level less than 0.1 micromol/L.

URINE OUTPUT

Check: Every 4 hours.
Aim: 400 mL/m²/4 hours (approx. 700 mL over 4 hours).
Furosemide: Administer 20-40 mg to maintain urine output.

FOLINIC ACID RESCUE

Start: 36 hour from start of methotrexate infusion.
Dose: 30 mg every 3 hours for 5 doses, then every 6 hours until methotrexate level is less than 0.1 micromol/L.
Administration: Give intravenous boluses for at least the first 4 doses then change to oral if the patient is compliant and not vomiting.

GLUCARPIDASE – reversal agent

NHS England will fund Glucarpidase (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m²)
- Who develop significant deterioration in renal function (>1.5x ULN and rising, or the presence of oliguria) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg
**CYCLE FREQUENCY**

Maximum of 4 complete cycles, i.e. 4 x R-HyperCVAD and 4 x R-MA alternating.

Start next course if neutrophil count is >1.0 x 10^9/L and platelet count is >60 x 10^9/L. Continue G-CSF until count is >1.0 x 10^9/L for 3 consecutive days. 24 hours after stopping G-CSF if neutrophil count is >1.0 x 10^9/L start next course. If the neutrophil count is >1.0 x 10^9/L but platelets are <60 x 10^9/L, continue G-CSF until neutrophil count is >1.0 x 10^9/L for 3 consecutive and await platelet recovery.

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**RESTAGING**

Re-stage with CT or CT PET neck, chest, abdomen, pelvis (with contrast) after maximum of 2 x R-hyperCVAD and 2 x R-MA alternating.

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**DOSE MODIFICATIONS**

**Hyper-CVAD**

**Cyclophosphamide:**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (mL/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;20</td>
<td>100%</td>
</tr>
<tr>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50%</td>
</tr>
</tbody>
</table>

Clinical decision – consider whether patient is being treated with high dose treatment.

**Doxorubicin:**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin micromol/L</td>
<td>Dose</td>
</tr>
<tr>
<td>20-51</td>
<td>50%</td>
</tr>
<tr>
<td>51-85</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;85</td>
<td>omit</td>
</tr>
<tr>
<td>If AST 2-3 x normal, give 75% dose</td>
<td></td>
</tr>
<tr>
<td>If AST &gt;3x ULN, give 50% dose</td>
<td></td>
</tr>
</tbody>
</table>

Doxorubicin maximum cumulative dose (additive to other anthracyclines):

- 450-550 mg/m² (in normal cardiac function)
- 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation).

Consider dose reduction in the event of cardiac impairment.
### Vincristine:

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose reduction necessary</td>
<td>Bilirubin 26-51 micromol/L or ALT/AST 60-180 u/L 50% dose</td>
</tr>
<tr>
<td></td>
<td>Bilirubin &gt;51 micromol/L &amp; normal ALT/AST 50% dose</td>
</tr>
<tr>
<td></td>
<td>Bilirubin &gt;51 micromol/L &amp; ALT/AST &gt;180 u/L omit</td>
</tr>
</tbody>
</table>

Vincristine: In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with a consultant.

### Methotrexate: clinical judgment discuss with consultant.

A fluid space, e.g. pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. High dose methotrexate should not be given in such cases.

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &gt; 80 mL/min 100% dose</td>
<td>Bilirubin &lt; 50 micromol/L and AST &lt; 180 u/L 100% dose</td>
</tr>
<tr>
<td>GFR 60 mL/min 65% dose</td>
<td>Bilirubin 51 - 85 micromol/L or AST &gt;180 75% dose</td>
</tr>
<tr>
<td>GFR 45 mL/min 50% dose</td>
<td>Bilirubin &gt; 85 micromol/L - contraindicated / discuss with consultant.</td>
</tr>
<tr>
<td>GFR &lt; 30 mL/min contra-indicated</td>
<td>High dose methotrexate expected to cause raised transaminases and occasionally hyperbilirubinemia, lasting up to 2 weeks after infusion, and are not considered toxicity requiring discontinuation of repeated administration of methotrexate.</td>
</tr>
</tbody>
</table>

Persistent hyperbilirubinemia and / or grade 3-4 raised transaminases for longer than 3 weeks should result in discontinuation of the drug. Contraindicated in severe hepatic impairment.

Reduce methotrexate dose by 50-75% if there is delayed excretion & / or nephrotoxicity with previous cycle.

### Cytarabine:

<table>
<thead>
<tr>
<th>Renal impairment (dose reduction may not be necessary)</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose 1-3 g/m² consider</td>
<td>Bilirubin &gt; 34 micromol/L give 50% dose</td>
</tr>
<tr>
<td>GFR 46-60 mL/min 60% dose</td>
<td>Escalate doses in subsequent cycles in the absence of toxicity.</td>
</tr>
<tr>
<td>GFR 31-45 mL/min 50% dose</td>
<td></td>
</tr>
<tr>
<td>GFR &lt; 30mL/min omit</td>
<td></td>
</tr>
</tbody>
</table>

Dexamethasone: Omit dexamethasone for severe proximal myopathy.

**INVESTIGATIONS**

FBC, U&Es, LFTs: as for in-patient care.
CONCURRENT MEDICATION

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>300 mg daily for 7 days starting 24-48 hours prior to chemotherapy (first course / cycle only)</td>
</tr>
<tr>
<td></td>
<td>Consider rasburicase if high risk for tumour lysis syndrome</td>
</tr>
<tr>
<td>Ranitidine (or PPI if specifically indicated - discuss with consultant)</td>
<td>Daily for the duration of treatment</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>50 mg daily for the duration of treatment</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>200 mg three times a day for duration of treatment and for 3 months after completion</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>5 mg three times a day PO as appropriate.</td>
</tr>
<tr>
<td>Prednisolone 0.5-1% eye drops</td>
<td>For MA cycles only</td>
</tr>
<tr>
<td>Or Dexamethasone 0.1% eye drops (depending on local formulary)</td>
<td>Starting from Day 3, one drop to each eye QDS. Continue for 5 days after cytarabine (due to risk of cytarabine-induced conjunctivitis). In the event of conjunctivitis, consider increasing the frequency to 2 hourly until resolution of symptoms. Liaison with ophthalmologists may be necessary in this situation.</td>
</tr>
<tr>
<td>Co-Trimoxazole</td>
<td>480 mg daily Mon, Wed, Fri after final cycle of chemotherapy, methotrexate level is &lt; 0.1 micromol/L and when neutrophils &gt;2x10^9/L. Continue for 3 months.</td>
</tr>
<tr>
<td></td>
<td>Patients MUST NOT receive co-trimoxazole during treatment. Consider pentamidine treatment if considered at risk from <em>Pneumocystis</em> infection.</td>
</tr>
<tr>
<td>G-CSF</td>
<td>As per local policy starting from Day 5.</td>
</tr>
</tbody>
</table>

A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.

**EMETIC RISK**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-CVAD</td>
<td>Days 1 to 4: High to moderate</td>
</tr>
<tr>
<td>MA</td>
<td>Day 1-2: High</td>
</tr>
<tr>
<td></td>
<td>Days 3 to 4: High to moderate</td>
</tr>
</tbody>
</table>
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cyclophosphamide may irritate the bladder. Encourage patient to drink a minimum of 3 litres per 24 hours.
Cardiotoxicity - monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity, e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Vincristine may cause neurotoxicity.
Rituximab - severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema.

EXTRAVASATION RISK

Cyclophosphamide: neutral
Cytarabine: neutral
Doxrubicin: vesicant
Etoposide: irritant
Methotrexate: inflammatory agent
Vincristine: vesicant
Rituximab: neutral

TREATMENT RELATED MORTALITY

2-5%.

REFERENCES