# R-Maxi CHOP and R-High Dose CYTARABINE (as Nordic protocol)

First-line use in Mantle Cell Lymphoma, for patients fit enough for PBSCT

**All patients should be screened for hepatitis B virus before starting treatment**

Treatment Summary:
Cycle 1: Maxi CHOP (no rituximab)
Cycle 2: Rituximab + High dose cytarabine
Cycle 3: Rituximab + Maxi CHOP
Cycle 4: Rituximab + High dose cytarabine
Cycle 5: Rituximab + Maxi CHOP
Cycle 6: Rituximab + High dose cytarabine, + additional rituximab Day 9

Drugs/Dosage:

***Cycle 1: Maxi-CHOP***

| | | | |
|---|---|---|---|
| **Cyclophosphamide** | 1200mg/m$^2$ | IV | Day 1 |
| **Doxorubicin** | 75mg/m$^2$ | IV | Day 1 |
| **Vincristine** | 1.4mg/m$^2$ (max 2mg) | IV | Day 1 |
| **Prednisolone** | 100mg (flat dose) | po daily | Day 1 to Day 5 |

***Cycles 2, 4 and 6: Rituximab + High dose Cytarabine***

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|---|---|---|---|
| **Rituximab** | 375mg/m$^2$ (dose 'banded' according to table below) | IV | Day 1 |
| **Cytarabine** | 3000mg/m$^2$ (2000mg/m$^2$ if age > 60 years) | IV | twice daily on Day 1 and Day 2 (4 doses total) |

***Cycles 3 and 5: Rituximab + Maxi-CHOP***

| | | | |
|---|---|---|---|
| **Rituximab** | 375mg/m$^2$ | IV | Day 1 |
| then | | | |
| **Cyclophosphamide** | 1200mg/m$^2$ | IV | Day 1 |
| **Doxorubicin** | 75mg/m$^2$ | IV | Day 1 |
| **Vincristine** | 1.4mg/m$^2$ (max 2mg) | IV | Day 1 |
| **Prednisolone** | 100mg (flat dose) | po daily | Day 1 to Day 5 |

***Cycle 6, Day 9 (with stem cell harvest):***

| | | | |
|---|---|---|---|
| **Rituximab** | 375mg/m$^2$ | IV | Day 9 |

**Premedication for rituximab:**

| | | |
|---|---|---|
| Paracetamol 1000mg | po | 60 minutes pre rituximab |
| Chlorphenamine 10mg | IV | 15 minutes pre rituximab |
| Dexamethasone 8mg | IV | 15 minutes before treatment |

IV dexamethasone may be omitted on Cycles 3 and 5 if Day 1 of oral prednisolone (100mg) is taken at least 30 minutes before start of rituximab infusion

**Other drugs:**
Allopurinol 300mg po daily, starting at least 24 hours before first dose – review after 3 weeks
Omeprazole 20mg od (or ranitidine) is recommended whilst treating with steroids
Corticosteroid eye drops e.g. Maxidex: one drop into each eye every 4 hours during high-dose cytarabine, and continuing for 5 days after cytarabine completed (7 days total)
Aciclovir as prophylaxis (400mg po bd)

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|---|---|
| Reason for Update: itraconazole removed; supportive drugs reviewed; ritux does not need to be given before 1st dose of cytarabine; rituximab dose banding updated to +/- 10% | Approved by Chair of Alliance TSSG: Dr A Laurie |
| Version: 4 | Date: 2.3.16 |
| Supersedes: Version 3 | Review Date: April 2018 |
| Prepared by: S Taylor | Checked by: C Tucker |

For Maxi-CHOP cycles: Mesna 800mg IV (slow bolus) immediately pre-CHOP, then 800mg po at 2 hours and again at 6 hours post-CHOP
G-CSF primary prophylaxis may be considered during the periods of neutropenia, according to Alliance guidelines for use of G-CSF
G-CSF mobilisation for harvesting to start on Day 5 of Cycle 6

Administration: Rituximab to be diluted in 500ml 0.9% sodium chloride & administered according to following instructions:

**First infusion:** start at 50mg/hr, according to infusion table below; escalate in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.
Monitor patient's vital signs at baseline and then every 30 minutes (before each increase in infusion rate) until end of infusion.

| | **Infusion Rate (mg/hour)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 50 | 100 | 150 | 200 | 250 | 300 | 350 | 400 |
| Rituximab 'banded' dose | **Infusion Rate (ml/hour) for rituximab in 500ml volume only** | | | | | | | |
| 450mg | 55 | 111 | 166 | 222 | 277 | 333 | 388 | 444 |
| 500mg | 50 | 100 | 150 | 200 | 250 | 300 | 350 | 400 |
| 600mg | 42 | 83 | 125 | 167 | 208 | 250 | 292 | 333 |
| 700mg | 36 | 71 | 107 | 143 | 178 | 214 | 250 | 286 |
| 800mg | 31 | 62 | 94 | 125 | 156 | 187 | 219 | 250 |
| 900mg | 28 | 56 | 83 | 111 | 139 | 167 | 194 | 222 |
| 1000mg | 25 | 50 | 75 | 100 | 125 | 150 | 175 | 200 |
| 1100mg | 23 | 45 | 68 | 90 | 114 | 136 | 159 | 182 |

**Subsequent Infusions:**

*** Patients who tolerated their first infusion at the standard recommended rate only ***
Give 20% of dose (i.e. 100ml) over 30 minutes, then the remaining 80% (i.e. 400ml) over 1 hour, to give a total infusion time of 90 minutes.
Monitor patient's vital signs at baseline, then every 30 minutes until end of infusion.

*** Patients who did not tolerate their first infusion at the standard rate ***
Administer and monitor as per first infusion, or at a slower rate if required.

If reactions occur at any time, stop the infusion. If symptoms improve, restart at half the previous infusion rate, and escalate as tolerated.

Doxorubicin injection via fast running infusion of 0.9% sodium chloride
Vincristine diluted in 50ml 0.9% sodium chloride and infused over 5-10 minutes
Cyclophosphamide in 250ml sodium chloride 0.9% infused over 30 minutes
Cytarabine in 500ml sodium chloride 0.9% infused over 1 hour
Prednisolone, available as 25mg, 20mg and 5mg tablets, with or after food

Frequency: 6 cycles in total, with alternating chemotherapy every 3 weeks, followed by stem cell harvest and BEAM PBSCT at the tertiary centre.
Stem cells should be mobilised off the back of Cycle 6 of R-high dose cytarabine.

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|---|---|
| Main Toxicities: | tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration); prolonged (> 7 days) myelosuppression, with risk of infections and haemorrhage (see Comments); alopecia; mucositis; cardiomyopathy; peripheral neuropathy; constipation; haemorrhagic cystitis; cytarabine syndrome (includes fever, myalgia, bone pain, rash and conjunctivitis); severe cytokine release syndrome – usually occurs within 1–2 hours of the first rituximab infusion (see Comments); ovarian failure; infertility |
| Anti- emetics: | Maxi-CHOP - highly emetogenic (but anti-emetic dexamethasone not needed)<br><br>High dose cytarabine – highly emetogenic |
| Extravasation: | doxorubicin & vincristine are vesicants |

| Regular Investigations: | | |
|---|---|---|
| | FBC | Day 1, and then, from Day 8 onwards, alternate days until WBC and platelets start to rise |
| | LFTs & U&Es | Day 1 |
| | LDH | Day 1 |
| | MUGA/echo | see Comments |
| | CT staging | after Cycle 4 |

Comments: Sperm banking if appropriate and time allows.

This regimen may cause prolonged myelosuppression, which should be supported according to local policies, including those for neutropenic sepsis, the use of blood products and isolation.

Omit rituximab if WBC > 25 x $10^9$/l, as increased risk of severe cytokine release syndrome. If in doubt, check with Consultant.

Full resuscitation equipment must be available, with immediate access to clinical staff trained in resuscitation for the first hour of the first rituximab infusion. Blood pressure, pulse, temperature and $O_2$ saturation must be measured and recorded at regular intervals as specified above.

Maximum cumulative dose of doxorubicin = 450 - 550mg/$m^2$. Check any previous anthracycline exposure.
A baseline MUGA scan/echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, gross or morbid obesity, smoker, ≥ 70 years old, previous exposure to anthracyclines, previous thoracic radiotherapy. If ejection fraction is less than 50%, an alternative regimen should be given.
MUGA/echo should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

**Dose Modifications**

Haematological Toxicity:

**Cycle 1:** There are no modifications for low blood counts.

**Day 1 of each subsequent cycle:**
Proceed once neutrophils > 1.0 x $10^9$/L and platelets > 100 x $10^9$/L.

Delay in count recovery after treatment should be managed according to local protocols / practice.
If low counts are thought to be due to disease, discuss with Consultant.

Renal Impairment:

| CrCl (ml/min) | Cyclophosphamide Dose |
|---|---|
| > 20 | Give 100% |
| 10 – 20 | Give 75% |
| < 10 | Give 50% |

Hepatic Impairment:

| ALT / AST | | Bilirubin (µmol/l) | Doxorubicin Dose |
|---|---|---|---|
| 2 – 3 x ULN | | - | Give 75% |
| > 3 x ULN | **or** | 20 – 50 | Give 50% |
| | | 51 – 85 | Give 25% |
| | | > 85 | Omit |

| Bilirubin (µmol/l) | | ALT / AST (units/l) | Vincristine Dose |
|---|---|---|---|
| 26 – 51 | **or** | 60 – 180 | Give 50% |
| > 51 | **and** | ≤ 180 | Give 50% |
| > 51 | **and** | > 180 | Omit |

| Bilirubin(µmol/L) | Cytarabine Dose |
|---|---|
| > 34 | Give 50% dose |

Neurotoxicity: Give 50% vincristine dose if Grade 2 motor and/or Grade 3 sensory toxicity. Omit with higher grades of toxicity. If in doubt, discuss with Consultant.

Patient Information: Macmillan leaflets for cyclophosphamide, doxorubicin, vincristine, cytarabine and rituximab (R-CHOP leaflet is not appropriate)

References:
North London Cancer Network Lymphoma Guidelines 2013
Geisler, C et al; Blood 2008; 112 (7): 2687 - 2693