MR – CHOP

DRUG Regimen

Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone and high dose methotrexate

INDICATION for use

High grade B cell lymphoma with synchronous CNS involvement, where R-CODOX-M contraindicated (including concurrent spinal disease)

Regimen

Day 1:

Rituximab 375mg/m^2 IV Infusion in 500ml 0.9% sodium chloride (infuse as per local protocol)

Cyclophosphamide 750mg/m^2 IV bolus

Doxorubicin 50mg/m^2 IV bolus

Vincristine 1.4mg/m^2 (max 2mg) IV infusion in 50ml 0.9% sodium chloride over 5 minutes

Prednisolone 40mg/m^2 ORAL DAILY for 5 days

Day 8 approx: (day 8 - 15)

Methotrexate 1.5 - 3.5g/m^2 IV (0.5g/m2 IV in 100mls 0.9% sodium chloride over 15 mins then 1-3g/m^2 iv in 500mls 0.9% sodium chloride over 3 hours)

Calcium folinate rescue start 24 hours after start of methotrexate infusion

Repeat every 21 days for 6 cycles

Give pegfilgrastim 6mg subcutaneous 24 hours after methotrexate infusion completed

Methotrexate Schedule

Fluids Day prior to MTX – ensure a fluid intake of 4 litres in the 24 hours prior to initiating the methotrexate schedule below. Give a stat dose of 3g sodium bicarbonate PO in the evening prior to starting methotrexate.

Day	Drug	Dose	Fluid	Route	Duration
1st day of MTX	Pre hydration Start 6am		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	4 hours
Check urine PH > 7 before proceeding to methotrexate					
1st day of MTX	10 AM Methotrexate	500mg/m^2	100ml 0.9% sodium chloride	IV	15 MIN
1st day of MTX	11 AM Methotrexate	3000mg/m^2	500ml 0.9% sodium chloride	IV	3 HRS
Concurrent fluids					
1st day of MTX	10 AM CONCURRENT		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 HRS
	Post hydration		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 HRS
	Post hydration		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6HRS
	Post Hydration		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 HRS
Day +1 MTX	Post Hydration		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 HRS
	Post Hydration		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 HRS
	Post Hydration		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 HRS
	Post Hydration		1000ml Glucose 4% sodium chloride 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 HRS

Nb the hydration bag runs concurrently with the methotrexate infusion. Methotrexate 3000mg/m^2 must stop after 3 hours even if some remaining.

Strict adherence to measuring urinary pH and ensuring levels are >7. (A urinary pH <7 (more acidic) reduces renal clearance of methotrexate and greatly increases toxicity and delays clearance).

If required give extra sodium bicarbonate (either 3g orally or 50ml of 8.4% IV).

Ensure that the fluid intake remains at 4.5 litres per 24 hours (minimum is 3 litres per 24 hours) until the methotrexate level is $<1x10^{-7}$M (0.1micromolar)

Aim for a diuresis of at least 150ml/hr - give IV Furosemide if necessary to maintain diuresis and maintain fluid balance.

Folinic Acid Rescue

Folinic acid rescue must start 24 hours after the start of the methotrexate

Time	Drug	Dose	frequency	route
At 24 hours	Folinic acid	15mg/m^2	stat	IV
24 - 48 hours	Folinic acid	15mg/m^2	Every 3 hours	IV
After 48 hours	Folinic acid	15mg/m^2	Every 6 hours until methotrexate level is less than 1.0 x 10^{-7} M (0.1micromolar(µmol/l))	IV

Timing of Methotrexate Levels

48 hours after start of Methotrexate

72 hours and then every 24 hours until plasma Methotrexate level less than 1x 10^{-7}M (0.1 micromolar)

Methotrexate levels are to be sent urgently to Alder Hey Hospital Biochemistry dept. Liaise with LTHTR lab and phone Alder Hey senior biochemist to check levels each day.

Take methotrexate levels every 24 hours until level < 0.1 µmol/l

Dosage of Folinic Acid if MTX levels high

If **48 hour** (from start of Methotrexate infusion) Methotrexate level is >2 x 10^{-5}M (20 micromolar) increase the dose of Folinic Acid (see below)

If **72 hour** level is > 2 x 10^{-6}M (2 micromolar) increase Folinic Acid and give iv as calculated below

If **72 hour** level is < 2 x 10^{-6}M (2 micromolar) continue with Folinic 15mg/m^2 iv 6 hourly until level is < 1 x 10^{-7}M (0.1 micromolar)

During methotrexate infusion and folinic acid rescue:

Continue to ensure urine pH is > 7 by giving stat doses of 3g sodium bicarbonate orally or 8.4% 50mls IV

Check daily U&Es, creatinine and alternate day FBC, LFTs

Monitor fluid balance carefully and give iv frusemide if fluid overload occurs or urine output falls to <150ml/hr

Calculation of folinic acid rescue on the basis of plasma methotrexate levels

	Plasma methotrexate level (µmol/l)				
Time after starting MTX	<0.1	0.1 - 2.0	2.0 - 20	20 - 100	>100
48hrs	none[a]	15mg/m^2 q6h[b]	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h
72hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h
96hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h
120hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h
>120hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h

a. No extra folinic acid required provided methotrexate levels are < 0.1µmol/l (10^{-7}M) at 48 hours
b. q6h = every 6 hours
c. At time points after 120 hrs folinic acid administration should be continued as recommended for time '120hrs after starting MTX'

Conversion table for methotrexate levels expressed in different units

molar (M)	µg/ml	ng/ml	µmol/l
1×10^{-3}	460.0		1013.0
2×10^{-4}	92.0		202.0
1×10^{-4}	46.0		101.0
2×10^{-5}	9.2		20.0
1×10^{-5}	4.6		10.1
2×10^{-6}	0.92		2.0
1×10^{-6}	0.46	460.0	1.01
2×10^{-7}	0.092	92.0	0.2
1×10^{-7}	0.046	46.0	0.10
2×10^{-8}	0.010	9.2	0.02

Cautions

Drug interactions:
The co-administration of Co-trimoxazole/Trimethoprim and methotrexate should be avoided as it can result in increased haematological toxicity.
NSAIDs and salicylates can reduce the clearance of methotrexate, resulting in increased toxicity.
Proton pump inhibitors can reduce clearance of methotrexate, resulting in increased toxicity. Change omeprazole/lansoprazole to ranitidine 150mg bd if gastric protection required.
Avoid other nephrotoxic drugs e.g. NSAIDs and Gentamicin

Penicillin based drugs can reduce clearance of methotrexate, resulting in increased toxicity. Avoid on days receiving methotrexate and until it is cleared (<0.1 micromolar). This includes avoiding TAZOCIN - if antibiotic monotherapy is needed for sepsis during methotrexate administration use Meropenem.

Comments:
If low Hb prior to treatment, blood transfusion should be completed prior to high dose Methotrexate (transfusing after high dose Methotrexate will delay the clearance of Methotrexate).

Patient to avoid fizzy drinks with citric acid –can lower urinary pH levels, which reduces renal clearance of methotrexate.

Allopurinol 300mg od to protect against tumour lysis with initial course.
DO NOT give Co-trimoxazole prophylaxis
H2 Antagonist for the first 7 days of each cycle

Prior to a course of treatment:

• Assess cardiac function by history & exam, ECG and CXR. If there is evidence of cardiac disease or risk

factors, prior anthracyclines or patient > 70yrs perform a MUGA scan. If LVEF< 50% discuss with consultant

• Check FBC. Patient must have adequate marrow reserve - neutrophils >1.0, platelets >75 unless cytopaenia is due to disease, e.g marrow infiltration, splenomegaly

• Check hepatitis B & C serology

• Check renal and liver function – see dose modification and discuss with consultant if abnormal

• If appropriate discuss possibility of pregnancy with female patients and need for contraception with both

male and female patients. Discuss risk of infertility - offer semen cryopreservation to male patients

• Written consent for course

Prior to each dose

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Only give methotrexate if serum creatinine is normal and creatinine clearance is >50ml/min/m^2

- Check FBC, U&Es, creat, LFTs - neuts must be >1.0 and plats > 100 – *see dose modifications*
- FBC, U&E, LFTs to be taken prior to each cycle (≤2days)
- Consider echocardiogram for patients with Cardiac History, diabetics >65yrs or patients age > 50 with hypertension, an abnormal ECG or who have had prior anthracycline therapy.
- Screen for Igs, viral Hepatitis and HIV prior to first cycle rituximab.
- Reassess response every 3 cycles

Prophylaxis for acute emesis	5HT antagonist
Prophylaxis for delayed emesis	5HT antagonist + metoclopramide 3-4 days

Dose modifications

Dose modification for neutropenia (unless due to lymphoma) and infection

- Neutrophils < 1.0 on day 1 Delay 1 week and proceed at 100% if they recover
- Neutrophils remain < 1.0 despite delay . Give GCSF for up to 1 week
- If no recovery despite GCSF Further treatment may be inappropriate - discuss with consultant
- If treatment is delayed > 1week, or >1 delay, or an episode of neutropenic sepsis and already on GCSF prophylaxis, reduce doses, omit methotrexate or stop regime.

Dose modification for thrombocytopenia (unless due to lymphoma)
Platelets <75 on day treatment due Delay cycle 1-2 weeks – if no recovery consider proceeding at 50-75% dose cyclophosphamide & doxorubicin or proceed at 100% dose with platelet support if needed - discuss with consultant

For cardiotoxicity
- If symptoms or signs of cardiac failure develop, discontinue doxorubicin and measure LVEF by MUGA scan. Inform consultant
- Consider substituting doxorubicin with etoposide (see 'modified CHOP-like' protocol) – discuss with consultant

For liver dysfunction (unless due to lymphoma)
- Bilirubin <1.5x upper limit of normal 100% dose doxorubicin
- Bilirubin 1.5 – 3 x upper limit of normal 50% dose doxorubicin
- Bilirubin > 3 x upper limit of normal Consider 25% dose or stopping CHOP

For renal dysfunction
- If Creat. Clearance <10ml/min Consider stopping CHOP or using 50% cyclophosphamide – discuss with consultant

Renal for methotrexate

Creatinine Clearance	Dose modification
60-80ml/min	Consider reducing dose to 65%
45-60ml/min	50% dose
<45ml/min	Clinical decision

For vincristine neurological toxicity
- Grade 2 motor (mild objective weakness interferingwith function but not with activities of daily living) or grade 3 sensory (sensory loss or paresthesia interfering with activities of daily living) toxicity: Reduce vincristine dose to 1mg
- Neurological toxicity increases despite reduction. Stop vincristine

SIDE EFFECTS:

Reduced immunity with possible life-threatening infection

Allergic reaction

Anaemia

Bruising/bleeding

Constipation

Diarrhoea

Impaired fertility

Flu-like symptoms

Hair loss

Heart damage

Lethargy

Kidney damage

Liver damage

Lung function changes

Written by	Dr Stephen Kennedy
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