Modified MACOP

For treatment of primary CNS NHL

Drugs/Dosages:

Doxorubicin	50mg/m^2	IV	Day 1 of Weeks 1, 3 & 5
Cyclophosphamide	350mg/m^2	IV	Day 1 of Weeks 1, 3 & 5
Methotrexate	1500mg/m^2	IV	Day 1 of Weeks 2, 4 & 6
Vincristine	1.4mg/m^2 (max 2mg)	IV	Day 1 of Weeks 2, 4 & 6
Prednisolone	60mg	po	once daily throughout, tailing off after 6 weeks

Starting 24 hours from start of methotrexate infusion:

Folinic acid	15mg/m^2 IV every 6 hours for 24 hours (adjusted if methotrexate levels indicate), then 30mg po every 6 hours until methotrexate undetectable in the blood. See Comments for further details.

Administration:

Doxorubicin and Vincristine are bolus injections given via fast running infusion 0.9% Sodium Chloride.
Cyclophosphamide is a bolus injection.
High dose methotrexate to be administered according to the following schedule (ideally start hydration at 10pm to ensure that methotrexate levels taken and measured within normal working hours):

Pre-Hydration:
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% IV over 4 hours
1 litre Glucose 5% + 70ml Sodium Bicarbonate 8.4% IV over 4 hours
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% IV over 4 hours

Check urine pH and only proceed with methotrexate once pH > 7 (see Comments)

Methotrexate in 1 litre Sodium Chloride 0.9% IV over 6 hours
Concurrent with:
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% IV over 6 hours

Post-Hydration:
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% IV + 20mmol KCl over 6 hours
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% IV + 20mmol KCl over 6 hours
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% + 20mmol KCl IV over 6 hours
Folinic acid to commence 24 hr after start of methotrexate infusion, as above
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% IV over 6 hours
1 litre Sodium Chloride 0.9% + 70ml Sodium Bicarbonate 8.4% IV over 6 hours

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Supersedes: All previous versions	Review date: February 2008
Prepared by Oncology Pharmacist: S Taylor	Checked by Network Pharmacist: Jacky Turner

Other Drugs: Use of proton pump inhibitor or H_2 receptor antagonist (e.g. ranitidine) is recommended whilst treating with steroids.
Allopurinol 300mg po daily – review after 2 weeks
PCP prophylaxis – prescribe according to unit practice/protocol.
(N.B. Co-trimoxazole should not be taken 24 hours prior to, and 24 hours post, methotrexate administration)

Drug Interactions: Avoid NSAIDs, salicylates & sulpha drugs (eg co-trimoxazole) concurrently with high dose methotrexate because they may delay excretion of methotrexate. Avoid concurrent nephrotoxic drugs, if possible. Penicillins have been known to interact with methotrexate.
If patient taking NSAIDs, they should be stopped if possible at least 72 hrs before the start of treatment until 48 hrs after methotrexate completed.

Frequency: a single cycle, given weekly for 6 weeks

Main Toxicities: myelosuppression; mucositis; alopecia; cardiomyopathy; peripheral neuropathy; steroid side effects; haemorrhagic cystitis; tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration); ovarian failure; infertility

Anti-emetics: Highly emetogenic on all weeks (but dexamethasone not required due to oral prednisolone throughout)

Extravasation: Doxorubicin & Vincristine are vesicants

Regular Investigations:		
	FBC	weekly
	U&Es	baseline, then Weeks 2, 4 and 6 (before methotrexate), and daily whilst in-patient (contact doctor if creatinine rises)
	LFTS	alternate weeks
	LDH	monthly
	Cr^{51}-EDTA or 24hr urine	baseline (see Comments)
	MUGA/echo	see Comments
	Methotrexate levels	24hr, 48hr and 72hr after start of methotrexate (see Comments)

Comments: Exclude third space fluids (ascites, pleural effusion) before starting methotrexate.

Repeat Cr^{51}-EDTA / 24 hour urine if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

On Weeks 2, 4 and 6, monitor fluid balance and urine pH carefully:
Methotrexate infusion should not start until urine pH is > 7. If urine pH < 7, give either 3g Bicarbonate orally or further IV Bicarbonate.
N.B. Acidic fruit juices should be avoided.

Weight should be recorded once daily and a strict fluid balance chart should be maintained. If there is a weight increase of 2kg, a positive fluid balance of 2 litres, or symptoms of fluid overload, furosemide 20-40mg po should be given.

Folinic acid rescue:
The schedule given above is normally sufficient unless problems are encountered with renal function or alkalinisation.
Methotrexate levels should be measured every 24 hours until methotrexate is undetectable in blood. Ensure arrangements have been made for taxi/courier as appropriate and pathology lab informed.
If methotrexate level remains high at 24 hours (i.e. > 5 µmol/l), then adjust folinic acid according to the following table:

Methotrexate Level (µmol/l)	Folinic Acid Dosing
> 50	1000mg/m^2 every 6 hours IV
5 – 50	200mg/m^2 every 6 hours IV
0.5 – 5	15 – 30 mg/m^2 every 6 hours IV or po
< 0.5	10mg/m^2 every 6 hours until undetectable

Maximum cumulative dose of Doxorubicin = 450 - 550mg/m^2
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. MUGA/echo should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

Dose Modifications

Haematological Toxicity: Proceed each week only once neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L. If low counts are thought to be due to marrow infiltration, discuss with Consultant.

Renal Impairment: Patient should have a measured GFR of ≥ 60ml/minute in order to proceed with high dose methotrexate.

GFR (ml/min)	Methotrexate Dose
> 80	Give 100%
60	Give 65%
< 60	This regimen not recommended

Hepatic Impairment:

Bilirubin (µmol/l)	Doxorubicin Dose
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**	Normal	Give 50%
> 51	**and**	> 180	Omit

Methotrexate is contraindicated in severe hepatic impairment.
Note that raised transaminases / bilirubin may occur for up to two weeks following each methotrexate dose, but this does not require discontinuation of further methotrexate unless transaminases are > 5 x ULN for more than 3 weeks.

Neurotoxicity:	Curative intent: Stop vincristine if patient experiences Grade 3 – 4 toxicity Without curative intent: Give 50% vincristine dose if Grade 2 motor and/or Grade 3 sensory toxicity If in doubt, discuss with Consultant.
Patient Information:	CancerBACUP leaflets for Methotrexate, Cyclophosphamide, Doxorubicin and Vincristine
Reference:	RMH NHS Trust, Neuro-Oncology Unit Protocol