SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

HIGH DOSE METHOTREXATE CNS NHL PROPHYLAXIS

PROTOCOL REF: MPHAHDMCN
(Version No. 1.0)

Approved for use in:

- High grade lymphoma with high risk of CNS involvement

Risk scoring is usually done on the basis of CNS IPI, or high risk may be defined by the number/ location of extranodal sites (as per BCSH GPP).

Caution in patients over 70 years of age, and/or with significant co-morbidities.

Blueteq not required

Dosage:

Drug	Dose	Route	Frequency
Methotrexate	**3500mg/m^2**	IV infusion	Day 1 (split into 500mg/m^2 over 15 minutes and then 3000mg/m^2 over 3 hours)

Normally 2 courses of intravenous methotrexate would be administered, after a full course of RCHOP chemotherapy (6 cycles).

Administration (+/- Counselling Points):

- **Co-trimoxazole and PPIs must be stopped at least 2 days prior to treatment**

- Piperacillin/Tazobactam (Tazocin®) should be avoided and meropenem used as first line treatment for febrile neutropenia following methotrexate infusion until methotrexate has cleared (level <0.1micromol/L)
- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.
- The hydration fluids on day 3 **MUST** start at least 6 hours prior to the methotrexate infusion.
- The patient's urine pH **MUST** be >7 before the methotrexate infusion is started.
- If urinary pH <7 during methotrexate infusion then additional sodium bicarbonate 8.4% 50mL can be infused separately by slow IV infusion (to be prescribed prn in Meditech).
- The second methotrexate infusion **MUST** start immediately after the loading dose.
- The blood sample needs to be sent to Alder Hey hospital in a taxi and then the lab at Alder Hey need to be rung for the result which should be documented in the medical notes.
- Folinic acid (calcium folinate) should be started 24 hours after the **start** of the methotrexate infusion
- The first methotrexate level should be taken 48 hours after the **start** of the methotrexate infusion. The methotrexate level should then be repeated daily until it is <0.1micromol/L at which point folinic acid rescue can stop.
- The dose of folinic acid (calcium folinate) may need to be modified 48 hours after the start of the methotrexate infusion in response to methotrexate levels (see High Dose Methotrexate Overview Protocol)
- If the serum creatinine increases by more than 25% from baseline then the folinic acid rescue should be escalated even before methotrexate level is known – seek urgent consultant advice.
- If severe methotrexate toxicity is suspected, then seek early consultant advice regarding the use of recombinant glucarpidase/carboxypeptidase.

Emetogenic risk

Moderately emetogenic

Supportive treatments:

High dose methotrexate pre-infusion medicines:

- Hydration fluids to start at least 6 hours before methotrexate
- Sodium bicarbonate 1g PO four times daily starting 24 hours pre-methotrexate
- Sodium bicarbonate 8.4% IV 50mL slow IV bolus prn (to be used if urinary pH <7)

Supportive medicines:

- Ondansetron PO 8mg BD
- Aciclovir 400mg PO twice daily
- Famotidine 20mg twice daily (if on existing PPI therapy, not needed routinely)
- Folinic acid IV 60mg every 6 hours to start 24 hours after the *start* of methotrexate infusion. See administration advice for further information.

Suspend co-trimoxazole and routine oral folic acid until methotrexate level <0.1micromol/L

Extravasation risk:

Methotrexate: non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

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.

Methotrexate			
Renal (ml/min) – use wright equation			
>60		100% dose	
40-60		50%	
<40		Omit	
Hepatic			
Bilirubin (micromol/L)		ALT (units/L)	Dose modification
<50	And	<180	100% dose
50-84	Or	≥180	75% dose
≥85			Omit

Interactions:

Methotrexate – See High Dose Methotrexate Overview Protocol

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**IV hydration:** **1L sodium chloride 0.18% / glucose 4% containing 20mmol potassium chloride and 50ml 8.4%sodium bicarbonate (bicarbonate to be added on the ward)**		**IV**	Start infusion 6 hours prior to methotrexate infusion,run at a rate of 250ml/hr for 6 hours, then run at a rate of 125ml/hr for 3 hours 15 minutes concurrent with methotrexate infusions, then run at a rate of 250ml/hr until desired methotrexate level is achieved (<0.1microlmol/l)
	Methotrexate	**500mg/m^2**	**IV**	In 100mls Sodium Chloride 0.9% over 15 minutes. The patient's urinary pH MUST be >7 before starting the infusion.
	Methotrexate	**3000mg/m^2**	**IV**	In 1000mls of Sodium Chloride 0.9% over 3 hours.

Main toxicities:

Bone marrow suppression, mucositis, stomatitis, nausea, vomiting, diarrhoea, skin irritation/sensitivity, renal impairment, AKI, deranged LFTs, interstitial pneumonitis.

Glucarpidase – Methotrexate reversal agent

NHS England will fund glucarpidase as a reversal agent for methotrexate (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m^2)

- 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

Refer to CCC glucarpidase protocol for further information

Investigations and treatment plan:

	Pre	All cycles Day 1	All cycles Day 2	Ongoing
Informed Consent	X			
Clinical Assessment	X			As clinically indicated or at the end of treatment
SACT Assessment (including PS and toxicity assessment)	X	X		Every cycle
FBC	X	X		Every cycle
U&E & LFTs & Magnesium	X	X		Every Cycle
CrCl (Wright)	X	X		Every cycle
CT scan	X			At the end of treatment and if clinically indicated
CSF analysis	X			
ECG				If clinically indicated
Blood pressure	X	X	X	If clinically indicated
Temperature, respiratory rate, pulse	X	X	X	If clinically indicated
Methotrexate levels			X	Daily until cleared
Weight	X	X	X	Every cycle
Height	X			
Pregnancy test	X			If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle one can proceed if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

If counts are below above values then treatment may be delayed at clinician discretion.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

See section entitled 'Dosing in Renal and Hepatic Impairment'

References:

1. https://www.medicines.org.uk/emc methotrexate (accessed April 2020)
2. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20: e201–08.

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
April 2023	V1.0	**Jennifer Gibson**	**New protocol**