High Dose Methotrexate (3000mg/m^2) Therapy 3 hour infusion (CNS prophylaxis)

Note: This regimen is used as an add-on for CNS prophylaxis. Patients should also be receiving a Systemic Anti-Cancer Therapy (SACT) regimen for lymphoma as per the consultant's treatment plan.

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
High grade lymphoma with high risk of CNS involvement.	C85	00439a	N/A

*This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

High dose methotrexate is administered as described below as CNS prophylaxis for 2-3 cycles in combination with a SACT regimen for high grade lymphoma.

- Treatment for CNS prophylaxis should be administered as early as possible as part of first-line therapy without compromising dose and time intensity of R-CHOP-like treatment
- Decisions on whether to intercalate or deliver at end of R-CHOP should be individualised, based on careful analysis of competing risks
    - If high dose methotrexate is intercalated with R-CHOP-21, the preferred scheduling appears to be midway through the cycle from day 10 onwards

Note:

- **Hydration, alkalinisation and folinic acid therapy required with high dose methotrexate (See Table below)**

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	Methotrexate [a,b]	3000mg/m^2	IV infusion	500mL 0.9% NaCl over 3 hours
2	Folinic acid	15mg/m^2	IV infusion	100mL 0.9% NaCl over 10 minutes. Commence 24 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L (See Table 1 below for calculation of dose of Folinic acid based on Methotrexate levels).

[a] Consider a dose reduction as appropriate for patients over 65 years of age.

[b]**Methotrexate:**
Hydration and Alkalinisation regimens are required with methotrexate. See below for suggested **or** Refer to local policy

GFR to be calculated prior to administration of methotrexate infusion**.**
Adequate hydration and urine output are essential for the rapid clearance of methotrexate

- Commence pre-hydration with sodium bicarbonate containing infusions at 125mLs/m^2/hr at least 6 hours prior to methotrexate infusion.
- **Hydration** with at least 3L/m^2/24 hours of **IV fluids** throughout treatment is essential until the methotrexate level is <1x 10^{-7} M (0.1micromol/L)
- Urine pH should be ≥ 7.0 prior to commencement and during the methotrexate and folinic acid rescue. Check urine pH at regular intervals (6 hourly)
- **Alkalinisation** can be achieved with 50mmol of sodium bicarbonate over 8 hours in 1000mL 0.9% NaCl.
  (This volume administered for alkalinisation is included in the total volume of hydration.)
  - Check urine pH at regular intervals (6 hourly)
  - If the target pH is not reached adjust the sodium bicarbonate concentration to maintain the urinary pH ≥ 7.0
- **Potassium** should be supplemented according to the local policy.
- Check **fluid balance** at regular intervals (4 hourly) through each day. (Furosemide may be administered if fluid output falls below 400mLs/m^2 in a 4 hour period).
- **Methotrexate levels** must be taken 48 hours, 72 hours, 96 hours and 120 hours as appropriate after commencement of the initial methotrexate infusion (book levels in advance with lab).

Continue alkalinisation, hydration and folinic acid rescue (Table 1) until methotrexate level is <1x 10^{-7} M (0.1micromol/L)

Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mLs or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide.

If furosemide is given, monitor pH for 2 hours post dose as this can cause pH to drop. If a drop in pH persists post 2 hours, increase alkinisation fluid rate from 8 hours to 6 hours until resolved.

Table1: Table for the Calculation of Folinic Acid Rescue on the basis of Methotrexate Levels

Time after starting Methotrexate infusion	Methotrexate Plasma Concentration micromol/L				
	<0.1	**0.1-2**	**2-20**	**20-100**	**>100**
48 hours	No folinic Acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours
72 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
96 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
120 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
If serum creatinine increases by more than 50% above baseline at 24 hours increase folinic acid rescue.					

At time points over 120 hours continue folinic acid as recommended for 120 hours.

ELIGIBILITY:

- High Grade Non-Hodgkin's Lymphoma with high risk of CNS involvement
  - CNS-IPI score of 4-6
  - Involvement of three or more extranodal sites irrespective of CNS-IPI
  - Involvement of certain anatomical sites: testicular, renal/adrenal, intravascular. Consider also if involvement of breast, uterus
  - Consultant/MDM decision
- Cr Cl ≥ 50mL/min recommended before administration of high-dose methotrexate

USE WITH CAUTION:

- In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment
- In patients with previous Hepatitis B/C infection that has not been eradicated as this may result in reactivation of virus and can lead to fulminant hepatic failure. Consult hepatology and consider anti-viral prophylaxis before use

EXCLUSIONS:

- Hypersensitivity to methotrexate or any of the excipients

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile,
- LDH, Uric acid
- Blood glucose
- Urine pH
- Baseline patient weight (dry weight) / daily weight
- Coagulation Screen including fibrinogen
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV
  *Hepatitis B reactivation: See Regimen Specific Complications

Regular tests:

- FBC, renal and liver profile prior to each treatment
- Urine pH
- Weight (dry weight) / daily weight
- Methotrexate levels (as per recommendations in the treatment table)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Renal and Hepatic Impairment:

Table 2: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment
Methotrexate	**CrCl (mL/min)**	**Dose**	Hepatic impairment: no need for dose adjustment is expected Bilirubin > 86 micromol/L: avoid use
	≥50	No dose adjustment is needed	
	20-50	50% of the original dose	
	<20	Not recommended. If unavoidable consider haemodialysis.	
	Haemodialysis	Not recommended. If unavoidable, 50% of the original dose can be dialysed with daily high flux dialysis.	
Dose modifications based on renal and hepatic impairment from Giraud et al.			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked Available on the NCCP website

Moderate (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link Available on the NCCP website

PREMEDICATIONS: None

OTHER SUPPORTIVE CARE:

PJP prophylaxis **(Refer to local policy). Consider interactions between methotrexate and co-trimoxazole.**

If co-trimoxazole cannot be avoided, cease PJP prophylaxis at least 48 hours prior to methotrexate infusion and recommence upon neutrophil recovery and clearance of methotrexate.

Mouth care **(Refer to local policy).**

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details

REGIMEN SPECIFIC COMPLICATIONS:

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.
- **High dose methotrexate and nephrotoxicity**: Monitoring of methotrexate levels is essential as delayed methotrexate excretion is potentially an emergency situation. Renal function must be evaluated prior to treatment and patients with creatinine clearance less than 50 mL/min should not receive high dose methotrexate. Methotrexate exits slowly from third space compartments (e.g. pleural effusions or ascites), resulting in a prolonged terminal plasma half-life and unexpected toxicity. **Hydration, alkalinisation and folinic acid therapy is required with high dose methotrexate to ensure adequate excretion.**

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. McKay P, Wilson MR, Chaganti S, Smith J, Fox CP, Cwynarski K; British Society of Haematology. The prevention of central nervous system relapse in diffuse large B-cell lymphoma: a British Society for Haematology good practice paper. Br J Haematol. 2020 Sep; 190(5):708-714. doi: 10.1111/bjh.16866. Epub 2020 Jul 15. PMID: 32433789.
2. Schmitz N et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in patients with Diffuse Large B-Cell Lymphoma treated with R-CHOP. J Clin Oncol 2016; 34:3150-3158
3. Abramson JS et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 2010; 116(18):4283-90**.**
4. UKALL14 Trial Protocol Appendix 15: Guideline for the administration of Intravenous High-Dose Methotrexate 10.1111/bjh.16866. Epub 2020 Jul 15. PMID: 32433789.
5. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
7. Methotrexate 100mg/mL Summary of Product Characteristics. Accessed Jan 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-061-002_27102023161846.pdf

Version	Date	Amendment	Approved By
1	01/11/2024		Dr Kamal Fadalla

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.