# INTRATHECAL METHOTREXATE +/- CYTARABINE +/_ HYDROCORTISONE

a) Intrathecal methotrexate for prophylaxis of CNS disease in Non-Hodgkin's Lymphoma with high risk of CNS relapse (see Comments)
b) Meningeal NHL at diagnosis

To be prescribed, supplied and administered in accordance with National Guidance on the Safe Administration of Intrathecal Chemotherapy

| Drugs/Dosage: | | | | |
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| | | Methotrexate | intrathecally | 12.5mg (in 0.5 ml) |
| | +/- | Cytarabine | intrathecally | 50mg (in 2.5 ml) |
| | +/- | Hydrocortisone sodium succinate | intrathecally | 50mg (in 1.0 ml) |

Administration: May only be administered by doctors registered on local Intrathecal Register and in accordance with National Guidance on the Safe Administration of Intrathecal Therapy. The nurse who checks the details on the syringes and is present during the procedure must also be on the local Intrathecal Register.
This protocol only applies to intrathecal administration via lumbar puncture.

Frequency: a) **prophylaxis in high risk aggressive NHL:**
Methotrexate alone; a suitable course of action would be a total of 3 - 4 doses[2], usually fortnightly, or every 3 weeks for patients on R-CHOP.
Patients with primary testicular lymphoma should receive a minimum of 4 doses[3].

b) **Meningeal NHL at diagnosis:**
Little evidence base, but a suggested course of action is:
"Triple therapy" twice a week for 4 weeks, then once a week for 4 weeks, then fortnightly for 4 weeks

Main Toxicities: MTX-associated acute and subacute chemical arachnoiditis (see Comments);
cytarabine-associated acute arachnoiditis;
risks due to procedure itself (infection, headache, aching of neck and lower back)

Anti- emetics: none routinely required (but nausea may occasionally occur)

| Regular Investigations: | | |
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| | FBC | within 24 hours of planned intrathecal procedure |
| | PT | within 24 hours of planned intrathecal procedure |
| | APTT | within 24 hours of planned intrathecal procedure |

Comments: All solutions used must be preservative-free

Patients at high risk of CNS relapse[3] include those with high grade lymphoma and either:

- raised LDH plus more than one extra-nodal localisation (spleen not regarded as extra-nodal, and two lesions in the same system are regarded as a single extra-nodal localisation)

or:

- anatomical sites - testicular, breast or involving epidural space

Intrathecal therapy must only be prescribed on an Intrathecal prescription chart

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| Reason for Update: indications reviewed/CNS relapse removed; high risk defined | Approved by Chair of Alliance TSSG: Dr A Laurie |
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| Prepared by: S Taylor | Checked by: C Tucker |

The following contra-indications should be excluded:

Previous hypersensitivity reaction to the prescribed drug(s)
Previous serious neurotoxicity from the drug
Raised intracranial pressure – cerebral or cerebellar herniation may occur
Thrombocytopenia or a raised PT or APTT make the lumbar puncture procedure risky.
If the platelets are < 50 x $10^9$/L, a platelet transfusion will be required immediately prior to the lumbar puncture. Ideally, platelet count should be rechecked after transfusion to confirm response.
Prolonged clotting times should be corrected before LP, although in practice FFP may only be given if the PT or APTT ratio is > 1.5.

**Neurotoxicity and methotrexate**

There are 3 distinct neurotoxic syndromes:

1. acute chemical arachnoiditis – severe headaches, nuchal rigidity, vomiting, fever, lethargy and inflammatory cell infiltrate in the CSF. This is rare, but starts 2-4 hours after the injection and lasts 12-72 hours. It usually responds to dexamethasone. These symptoms can be diminished in future by decreasing the methotrexate dose or changing to an alternative, usually cytarabine.
2. subacute chemical arachnoiditis – occurs in 10% patients after 3rd or 4th dose of intrathecal methotrexate. It consists of motor paralysis, cranial nerve palsies, and seizures or coma or both. A change in therapy is absolutely indicated because continued methotrexate treatment may result in death.
3. chronic demyelinating encephalopathy – typically occurring months to years after receiving intrathecal methotrexate.

## Dose Modifications

Haematological Toxicity:

Platelets < 50 x $10^9$/L - lumbar puncture not to be performed[1].
If necessary, a platelet transfusion may be given immediately before LP as cover (see Comments).

Prolonged APTT or PT – increased risk of haemorrhage with lumbar puncture. It may be necessary to consider using Vitamin K and FFP if patient on anti-coagulation therapy, to minimise hazard (see Comments).

There is some systemic absorption of intrathecal chemotherapy, which may contribute to any neutropenia.

Renal Impairment: No dose modifications required

Hepatic Impairment: No dose modifications required

Patient Information: Macmillan leaflet: Lumbar puncture (& intrathecal chemotherapy)
Macmillan leaflet for Methotrexate
The patient must be fully informed regarding the drug he/she will receive intrathecally, consent must be obtained, and patients may take part in the checking procedure at the time of administration, in line with the recommendations in the National Guidance.

References:

National Guidance on the Safe Administration of Intrathecal Chemotherapy, HSC 2008/001
[1]Schiffer, C et al; JCO 2001; 19 (5): 1519 - 1538
[2]Boehme, V et al; Blood 2009; 113 (17): 3896 – 3902
[3]McMillan, A et al; Br J Haem 2013; 163: 168 - 181

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