INTRATHECAL METHOTREXATE +/- CYTARABINE +/- HYDROCORTISONE

Treatment and prophylaxis of CNS disease in Non Hodgkins Lymphoma
To be prescribed, supplied and administered in accordance with National Guidance on the Safe Administration of Intrathecal Chemotherapy

Drugs/Dosage:	Methotrexate	intrathecally	12.5mg
	Cytarabine	intrathecally	50mg
	Hydrocortisone sodium succinate	intrathecally	50mg

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 syringes and is present during the procedure must also be on the local Intrathecal Register.
Intrathecal administration can be via lumbar puncture **or** intraventricular administration using an Ommaya reservoir.

Frequency: Little evidence base, but the following is a suggested suitable course of action:
For meningeal NHL (at diagnosis):
"triple therapy" twice a week for 4 weeks, then once a week for 4 weeks, then fortnightly for 4 weeks
For prophylaxis of high risk aggressive NHL:
Methotrexate alone, for a total of 4 - 6 doses (usually fortnightly)
For CNS relapse:
Methotrexate alone (or cytarabine if methotrexate inappropriate) up to three times weekly

Main Toxicities: acute and subacute chemical arachnoiditis (methotrexate – see Comments); acute arachnoiditis (cytarabine); 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:	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

Intrathecal therapy must only be prescribed on an Intrathecal prescription chart

The following contra-indications should be excluded:
Hypersensitivity reactions to any of the drugs
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.

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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: CancerBACUP leaflet: Lumbar puncture (& intrathecal chemotherapy)
CancerBACUP leaflets for Methotrexate and Cytarabine as appropriate
The patient must be fully informed regarding the drugs 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:
Updated National Guidance on the Safe Administration of Intrathecal Chemotherapy HSC 2003/010; Department of Health website www.dh.gov.uk
Oxford Handbook of Clinical Haematology, University Press, Oxford, 1998
[1]Schiffer et al, 2001; Platelet Transfusion for Patients with Cancer: Clinical Practice Guidelines of the American Society of Clinical Oncology

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