Lymphomatous meningitis

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Malignant meningitis is a rare but devastating complication of neoplastic disease. It occurs most commonly in lung, melanoma, breast, primary brain tumours and haematological disorders. It is almost always a diffuse process even when it appears to be limited. The outcome is almost always fatal.

Lymphomatous meningitis is generally accepted to occur in about 5% of diffuse large B-cell lymphomas, though rarely at presentation, it is more usual at relapse. The incidence is much higher in Burkitt's, HIV associated lymphoma, HTLV-1 associated lymphoma, PTLDs and lymphoblastic lymphoma. There is disagreement as to those patients *at risk* of developing lymphomatous meningitis who may merit prophylaxis. There is a view that all lymphoma patients with a high IPI score are at risk, whilst others have attempted to identify involvement of specific extra-nodal sites such as bone marrow, breast, testicular or the gastro-intestinal tract. It is generally agreed that patients with widespread disease and high serum lactate dehydrogenase levels are at greatest risk.

The prognosis of lymphomatous meningitis is very poor with survival measured in a few months. In the majority of patients' therapy should be given to improve performance status and aim to prevent neurological progression.

Chemotherapy has become the mainstay of treatment for lymphomatous meningitis. The effectiveness of systemic chemotherapy is severely limited by the fact that many drugs are unable to penetrate the central nervous system because of the protection afforded by the blood brain barrier. Direct puncture into the cerebrospinal fluid (CSF) achieves cytotoxic levels of chemotherapy. Intra-thecal methotrexate is the most frequently used drug for the treatment of lymphomatous meningitis. Methotrexate is not metabolized within the CSF and relies on absorption by the choroid plexus into the systemic circulation where it may lead to myelosuppression in patients with poor marrow reserve, renal failure, patients with pleural fluid etc. Folinic acid may be given in an attempt to reduce systemic toxicity. Intrathecal methotrexate may cause leucoencephalopathy, particularly in patients with interruption of CSF flow and in patients receiving concurrent radiation. Intra-thecal cytarabine is usually administered at a dose of 50-70 mg twice weekly, followed by weekly and then monthly. The half-life of cytarabine in the CSF is very short and of the order of 2-4 hours with therapeutic levels being maintained for about 24 hours after each injection. High dose systemic chemotherapy relies on lipid solubility to overcome the blood brain barrier. High dose systemic methotrexate is administered in doses of 2-8 g/m^2 with alkalinisation, hydration and folinic acid rescue. It is generally accepted that CSF levels are much higher after direct intra-thecal puncture rather than following administration of high dose systemic chemotherapy, even so, there is some evidence of greater efficacy over IT treatment; though, high dose systemic treatment is costly and involves lengthy hospital stays. High dose cytarabine leads to CSF levels approximately 20% of systemic levels; the usual dose being 2-3 g/m^2 every 12 hrs. There are some important toxic effects associated with the use of high dose cytarabine including nausea and vomiting, mucositis, myelosuppression and cerebellar toxicity.

Emerging strategies include new drugs such as intra-thecal interferon and intrathecal Rituximab and novel delivery systems such as slow release cytarabine arabinoside. The trials and data on Depocyte will be discussed. Results show an improvement in the response rate and time to neurological progression. Slow release liposomal cytarabine result in a continuous exposure of tumour cells to cytarabine when administered once every two weeks. Depocyte, is a sterile sustained release preparation that is now licensed for use in lymphomatous meningitis in Europe and the

USA It is available in 5 mL, ready to use, vials containing 50 mg of cytarabine. Single dose administratioin of Depocyte 50mg maintains cytotoxic doses of the drug for two weeks. Lymphomatous meningitis is a relatively rare disorder. There are no controlled trials looking at the treatment of lymphomatous meningitis so definite treatment recommendations for treatment or prophylaxis are difficult to make. Treatment decisions are difficult and must be backed up by careful diagnostic evaluation including CSF examination, including clonality testing by immunophenotyping together with cytogenetic and molecular studies if necessary. Complete imaging of the entire neuroaxis is indicated using contrast enhanced MRI. Treatment is palliative and should be combined with general supportive measures. The introduction of sustained release intra-thecal ara-C is a promising advance in the treatment of this difficult disorder.

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