Methotrexate

Methotrexate, abbreviated MTX and formerly known as amethopterin, is an antimetabolite and antifolate drug.

It is used in treatment of cancer, autoimmune diseases, ectopic pregnancy, and for the induction of medical abortions.

It acts by inhibiting the metabolism of folic acid.

Methotrexate began to replace the more toxic antifolate aminopterin starting in the 1950s. The drug was originally synthesised by the Indian biochemist Yellapragada Subbarow and clinically developed by the American paediatrician Sidney Farber.

It is on the World Health Organization's List of Essential Medicines, a list of the most important medications needed in a basic health system.

The folate-antagonist methotrexate (HD-MTX) is integral to induction chemotherapy for Primary central nervous system lymphoma; however, it can be associated with leukoencephalopathy. Methylenetetrahydrofolate-reductase (MTHFR) is involved in intracellular folate depletion.

Karschnia et al. assessed whether MTHFR polymorphisms affect the risk for leukoencephalopathy.

They retrospectively searched the database at the Massachusetts General Hospital for newly diagnosed PCNSL treated with HD-MTX (without radiotherapy nor intrathecal chemotherapy).

Among 68 PCNSL patients, MTHFR polymorphisms were found in 60 individuals (88.2%) including a 677C→T genotype, a 1298A→C genotype, or a combined 677C→T/1298A→C genotype. Neither MTX clearance nor response to induction therapy was affected by specific genotypes, and complete response was achieved in 72.1% of patients by HD-MTX-based induction. However, the 1298A→C genotype was associated with increased frequency and severity of leukoencephalopathy over time (odds ratio: 4.0, CI 1.5-11.4). Such genotype predicted treatment-induced leukoencephalopathy with a sensitivity of 71.0% and a specificity of 62.2% (AUC: 0.67, CI 0.5-0.8; p=0.019). While progression-free survival did not differ in genotype-based subgroups, overall survival was lower for the 1298A→C genotype.

The MTHFR 1298A→C genotype may serve to identify PCNSL patients at elevated risk for HD-MTX-induced leukoencephalopathy. This appears to translate into reduced survival, potentially due to decreased functional status [1)].

Primary craniosynostosis is usually a prenatal deformity. Etiologies of secondary craniosynostosis include: metabolic (rickets, hyperthyroidism…), toxic (drugs such as phenytoin, valproate, methotrexate…),

Indications

A chemotherapeutic agent used for CNS tumors

see Methotrexate for Primary central nervous system lymphoma.

Treatment options for unresponsive neurosarcoidosis cases include methotrexate.

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see Chemotherapy for Medulloblastoma

Granulomatosis with polyangiitis treatment

Patients with leptomeningeal carcinomatosis face a particularly grim prognosis. Current treatment consists of intrathecal delivery of methotrexate (MTX) or cytosine arabinoside (Ara-C) via ventricular access device (Ommaya reservoir) or lumbar puncture. Yet despite these interventions, the median survival after diagnosis is only 4-7 months [2].

A catheter was surgically placed into the fourth ventricle and attached to a ventricular access device. Cerebrospinal fluid (CSF) flow was confirmed by CINE MRI postoperatively. Each cycle consisted of 4 consecutive daily methotrexate infusions (2 milligrams). Disease response was monitored with serial MRI scans and CSF cytologic analysis. Trough CSF methotrexate levels were sampled. Five patients (3 with medulloblastoma and 2 with ependymoma) received 18, 18, 12, 9, and 3 cycles, respectively. There were no serious adverse events or new neurological deficits attributed to methotrexate. Two additional enrolled patients were withdrawn prior to planned infusions due to rapid disease progression. Median serum methotrexate level 4 h after infusion was 0.04 µmol/L. Range was 0.02-0.13 µmol/L. Median trough CSF methotrexate level 24 h after infusion was 3.18 µmol/L (range 0.53-212.36 µmol/L). All three patients with medulloblastoma had partial response or stable disease until one patient had progressive disease after cycle 18. Both patients with ependymoma had progressive disease after 9 and 3 cycles, respectively. Low-dose methotrexate can be infused into the fourth ventricle without causing neurological toxicity. Some patients with recurrent medulloblastoma experience a beneficial anti-tumor effect both within the fourth ventricle and at distant sites [3].

Arthrorheumatism with methotrexate-associated lymphoproliferative disorder in the brain [4].

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4)
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