Methotrexate for Primary central nervous system lymphoma

In neurooncology and onco-hematology, intraventricular injection of chemotherapeutic agents (most typically, methotrexate) is an inevitable part of many protocols for treating patients with malignant tumors of the CNS, neuroleukemia, CNS lymphomas and some other disorders.

High-dose MTX is associated with a high proportion of radiographic responses and a low proportion of grade III/IV toxicity in patients 70 or more years of age. High-dose MTX should be considered as a feasible treatment option in elderly patients with PCNSL [1)].

MTX-monotherapy is tolerable in terms of adverse effects and still considered as a treatment option in patients with PCNSL. However, an additional therapeutic option should be prepared for non-CR responders to induction chemotherapy [2)].

The addition of intraventricular MTX (rather than just intrathecal via LP) delivered through a Ommaya reservoir (6 doses of 12 mg twice a week, with IV leucovorin rescue) may result in even better survival [3)]

In the event of an intrathecal MTX overdose (OD), interventions recommended [4)] :

ODs of up to 85 mg can be well tolerated with little sequelae; immediate LP with drainage of CSF can remove a substantial portion of the drug (removing 15 ml of CSF can eliminate ≈ 20–30% of the MTX within 2 hrs of OD). This can be followed by ventriculolumbar perfusion over several hours using 240 ml of warmed isotonic preservative-free saline entering through the ventricular reservoir and exiting through a External lumbar cerebrospinal fluid drainage. For major OD of > 500 mg, add intrathecal administration of 2,000 U of carboxypeptidase G2 (an enzyme that inactivates MTX). In cases of MTX OD, systemic toxicity should be prevented by treating with IV dexamethasone and IV (not IT) leucovorin.

Therapeutic Outcomes and Toxicity of High-Dose Methotrexate-Based Chemotherapy for Elderly Patients with Primary Central Nervous System Lymphoma: A Report on Six Cases. [5)].

A study provides Class III evidence that in immunocompetent patients with primary CNS lymphomas (PCNSLs), high-dose methotrexate (HD-MTX) plus rituximab compared with HD-MTX alone improves complete response (CR) and overall survival rates [6)].

Case series

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 [7].

Yoon et al. presented the experiences with high-dose methotrexate (HD-MTX) monotherapy for immunocompetent patients with PCNSL at three institutions and investigate factors related to survival.

PCNSL patients, who were histologically confirmed with diffuse large B cells and treated with HD-MTX monotherapy from 2001 to 2016, were retrospectively reviewed. Patients underwent induction chemotherapy with 8 g/m2 of MTX every 10 days (maximum three cycles). Maintenance chemotherapy of 3.5 g/m2 of MTX (maximum six cycles) was selectively performed depending on the response to induction chemotherapy.

A total of 67 patients were included. Although seven patients discontinued induction chemotherapy because of MTX toxicity, 40 (59.7%) patients showed a complete response (CR) to induction chemotherapy. Twenty-six (38.8%) and three (4.5%) patients showed a CR and partial response, respectively, after maintenance chemotherapy. Forty-one patients with recurrence or progression following HD-MTX underwent second-line treatment. Progression-free survival rates were 43% and 24% at 1 and 2 years, respectively. The median overall survival was 40.3 months. In a multivariate analysis, a radiological CR to induction chemotherapy was a significant factor related to prolonged progression-free survival and overall survival ($P < 0.05$).

MTX-monotherapy is tolerable in terms of adverse effects and still considered as a treatment option in patients with PCNSL. However, an additional therapeutic option should be prepared for non-CR responders to induction chemotherapy [8].

A single-institution retrospective analysis was performed for 12 patients with newly diagnosed PCNSL treated with combined high-dose methotrexate (HD-MTX) and RTX. MTX was administered biweekly at 8 g/m2/dose until a complete response (CR) was achieved or for a maximum of eight doses. RTX was provided for a total of eight weekly doses at 375 mg/m2/dose. Following a median of 11 cycles of MTX, the radiographic overall response rate was 91% and the CR rate was 58%. A CR was achieved after a median 6 cycles of MTX. The median progression-free survival time was 22 months and the median overall survival time has not yet been attained. These results compare favorably to single-agent HD-MTX and suggest a role for immunochemotherapy in the treatment of PCNSL [9].

Zhu et al. studied the response and adverse effects of intravenous high-dose MTX in patients who were 70 or more years of age at the time of diagnosis. They identified 31 patients diagnosed with PCNSL at age > or =70 years (median, 74 years) who were treated with high-dose MTX (3.5-8 g/m(2)) as initial therapy from 1992 through 2006. The best response to MTX was determined by contrast-enhanced MRI. Toxicity was analyzed by chart review. These 31 patients received a total of 303 cycles of MTX (median, eight cycles per patient). Overall, 87.9% of the cycles required dose reduction because of impaired creatinine clearance. In 30 evaluable patients, the overall radiographic response rate was 96.7%, with 18 complete responses (60%) and 11 partial responses (36.7%). Progression-free survival and overall survivals were 7.1 months and 37 months, respectively. Grade I-IV toxicities were observed in 27 of 31 patients and included gastrointestinal disturbances in 58% (3.2% grade III), hematological complications in 80.6% (6.5% grade III), and renal toxicity in 29% (0% grade III/IV). High-dose MTX is associated with a high proportion of radiographic responses and a low proportion of grade III/IV toxicity in patients 70 or more years of age. High-dose MTX should be considered as a feasible treatment option in elderly patients with PCNSL [10].

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