

Intrathecal Methotrexate and Acute Neurotoxicity: A Painful Experience

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ABSTRACT

Intrathecal treatment with methotrexate, an essential chemotherapeutic for both prophylaxis and treatment of central nervous system involvement of leukemia, may be associated with local neurotoxicity and/or systemic toxicity. Signs of acute neurotoxicity include confusion, disorientation, seizures, aphasia, ataxia, dysarthria, paresis and even paralysis. Presented here is a case of a 58 year old patient with acute lymphoblastic leukemia who developed acute neurotoxicity after her 13th dose of intrathecal methotrexate. Available treatment options are also discussed.

Key Words: Intrathecal methotrexate, Central nervous system involvement, Acute neurotoxicity, Acute lymphoblastic leukemia

ÖZET

İntratekal Metotreksat ve Nörotoksisite: Ağrılı Bir Deneyim

Lösemilerin santral sinir sistemi tutulum açısından hem profilaksisinde hem de tedavisinde yeri olan intratekal metotreksat tedavisi, lokal nörotoksisite ve/veya sistemik toksisiteye neden olabilir. Akut nörotoksisite bulguları, konfüzyon, dezoryantasyon, nöbet, afazi, ataksi, dizartri, parezi ve paralizi şeklinde kendini gösterebilir. Sunduğumuz vaka, 58 yaşında, akut lenfoblastik lösemi tanısı ile almakta olduğu intratekal metotreksatın 13. dozundan sonra akut nörotoksisite gelişti. Bu durumda tercih edilebilecek uygun tedavileri de tartışmaya çalıştık.

Anahtar Kelimeler: İntratekal metotreksat, Santral sinir sistemi tutulumu, Akut nörotoksisite, Akut lenfoblastik lösemi

INTRODUCTION

Intrathecal treatment with methotrexate (MTX) or cytosine arabinoside is a crucial step for prophylaxis and treatment of central nervous system involvement of leukemia (1). Intrathecal MTX therapy may be associated with acute local neurotoxicity and/or systemic toxicity (1,2).

CASE REPORT

A 58-year-old woman presenting with fever and abdominal pain had severe anemia. A peripheral blood smear revealed 95% blastic cells. Bone marrow aspiration and biopsy confirmed the diagnosis of acute lymphoblastic leukemia. Translocation t(9;22) was negative. Treatment with hyperCVAD chemotherapy protocol (3) was initiated, including 2nd and 8th day intrathecal MTX administration for each cycle. During the 7th cycle, approximately 15 minutes after the 13th intrathecal MTX administration, the patient developed nausea and vomiting. Her arterial blood pressure rose to 200/100 mmHg. She developed severe pelvic and perineal pain within minutes, followed by urinary incontinence which resolved spontaneously. The patient complained of lower abdominal discomfort within an hour. On physical examination, an ensuant globe vesicale was recognized that prompting internal urinary catheterization. Her pelvic/perineal pain failed to respond to both non-steroid and narcotic analgesics immediately, and all her symptoms resolved completely about 4 hours later with no permanent lateralizing neurological deficits. Her findings were attributed to MTX (Naranjo ADR probability scale = 6), and it was verified that there was no overdose.

DISCUSSION

Signs of acute neurotoxicity with intrathecal MTX include confusion, disorientation, seizures, aphasia, ataxia, dysarthria, paresis and even paralysis, and are estimated to occur in 10-20% of patients (4, 5). The mechanism for MTX mediated neurotoxicity is still unclear. It is probably caused by folate deficiency or hypothetically elevated levels of homocystein which is excitatory aminoacid neurotransmitter metabolites (homocysteic acid and cysteine sulfiric acid) (6). The most emphasized com-

plication is progressive myelopathy characterized by progressive leg weakness, ascending sensory neuropathy and incontinence. However, most of the reported cases were from the pediatric age group, with Bay et al (7) reporting on 6 children who developed urinary incontinence followed by globe vesicale after intrathecal therapy. While these finding resolved within 2 hours in four of the patients, the other two were still unable to walk by the first month and their urinary incontinence never improved. Such findings have rarely been reported in the adult population. Interestingly, although associated with large doses, and especially a history of multiple injections (5-53 times), neurologic side effects have also been documented in children and adolescents after a single dose of intrathecal or systemic MTX treatment (6).

There is no consensus on the optimum treatment of acute neurotoxicity. Many advocate the exchange of CSF with isotonic saline (8, 9), with varying success reported with intrathecal administration of carboxypeptidase G2 (CPDG2), an enzyme that inactivates MTX (9,10). Our patient's pain failed to respond to conventional analgesics, and although the patient refused any further intervention, a more aggressive course of action should always be implemented for earlier relief and perhaps the prevention of permanent neurological sequela.

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