Acute Transient Cerebral Toxicity Associated with Administration of High-Dose Methotrexate

A Case Report

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Key Words

High-dose methotrexate · Neurotoxicity · Acute transient cerebral dysfunction

Abstract

Objective: To report the first case of transient central nervous system toxicity after administration of high-dose methotrexate (HDMTX) in the Middle East. **Clinical Presentation:** A 10-year-old boy was diagnosed with osteosarcoma of the proximal end of the left tibia. He underwent primary amputation and was started on adjuvant chemotherapy, which included administration of HDMTX. He developed acute cerebral toxicity after the 5th dose of HDMTX in the form of diplopia, seizures and disorientation. He recovered completely without any complication or neurological sequelae. **Conclusion:** The acute cerebral toxicity associated with HDMTX was completely reversible and without any sequelae.

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Introduction

Methotrexate (MTX) is an important cytostatic drug in cancer chemotherapy. It belongs to the group of ‘anti-metabolites’, which directly interfere with DNA synthe-

sis. High-dose methotrexate (HDMTX) is now commonly used in the treatment of acute lymphoblastic leukemia, lymphoma and osteosarcoma. In addition to common hematological and gastrointestinal complications, therapy with HDMTX is occasionally associated with central nervous system (CNS) toxicity. Acute CNS toxicity sometimes presents in the form of acute transient cerebral dysfunction, which may manifest in confusion, disorientation, seizures, and focal neurological deficits [1–3]. These symptoms are usually completely reversible with no permanent sequelae.

We report a patient with osteosarcoma, who had an episode of acute transient cerebral dysfunction following HDMTX and complete recovery after supportive therapy.

Case Report

A 10-year-old boy was diagnosed with osteosarcoma of the left proximal tibia in March 2002. The diagnosis was confirmed by open biopsy. Staging workup did not reveal any metastasis. He was referred to the Unit of Pediatric Oncology, Kuwait Cancer Control Center, Kuwait for neoadjuvant chemotherapy. However, for personal reasons the family delayed the start of therapy by more than 3 months. By the time they agreed to start chemotherapy, the tumor had progressed considerably with superficial skin necrosis, bleeding and secondary infection. In view of these complications, there was a change in the plan for initial treatment and he underwent pri-

mary amputation (above knee) of the left leg on 05.06.2002. Following recovery from surgery he was started on adjuvant chemotherapy according to the CCG 7921/POG 9359 protocol. He received his first course of chemotherapy (cisplatin and Adriamycin) on 23.06.02. He tolerated the treatment chemotherapy well and received week 15 chemotherapy (5th HDMTX, 12 g/m², and calcium leucovorine) on 03.11.02. He was to be discharged on the morning of 06.11.02 after MTX level was <0.1 µg, but he suddenly complained of diplopia followed by one episode of seizures. On examination, he was semiconscious and disoriented with stable vitals. An intravenous line was set up, oropharyngeal suction was commenced and oxygen was given by facemask. An urgent CT scan of the brain was carried out, which was essentially normal. Blood chemistry and hemogram were also within the normal range. He was moved to the ICU for supportive care. The pediatric neurologist advised to manage him symptomatically. Ophthalmological examinations revealed a mild abnormality in the conjugate movements of the eyes, with essentially normal fundi. He recovered completely from this episode with in the next 48 h without any serious neurological sequelae. Subsequently he underwent EEG on 11.11.02, which recorded background activity of lower voltage in the central leads, more over the left side with a few sharp waves in the left posterior leads of no significance. He also underwent an MRI scan (17.11.02) of the brain on the advise of the pediatric neurologist, which was also normal. He completed his subsequent courses of chemotherapy without any further complication. However, HDMTX was not given as a precautionary measure because of hesitancy on the part of the family. One year following this episode the patient is well with no evidence of recurrent disease or any neurological deficit.

Discussion

The incidence of neurological complications after HDMTX has been reported in the range of 5–15% [1–5]. These complications have been divided in to acute, sub-acute or delayed complications [6, 7]. The majority of the acute complications are transient, presenting as acute stroke with encephalopathy and invariably results in full recovery with no long-term neurological sequelae. It has been named variously as ‘transient encephalopathy’ [1], ‘transient cerebral dysfunction’ [4], or ‘temporary neurologic dysfunction’ [8]. The pharmacokinetics of MTX is not related to such episodes [3, 9], and our patient had normal MTX levels. The imaging studies are essentially normal, as in our patient, who had a normal CT scan and MRI (which was done at a later date). Anselm et al. [9] reported focal area of hyperintensity on MRI, while Gay et al. [10] reported evidence of leukoencephalopathy on MRI studies in patients given HDMTX along with Ara-C. The EEG studies carried out in this case showed some nonspecific changes, which have also been reported by Kiu et al. [3] and Walker et al. [4], Jaffe et al. [8], but their significance is not clear. The etiology of acute encephalopathy

remains unknown in most cases. Various authors have postulated a possible mechanism for these complications. Fritsch et al. [1] implicated this transient cerebral dysfunction to embolization by tumor tissue, while Allen et al. [2] attributed it to leukoencephalopathy directly related to MTX or an embolic cerebral vasculopathy because of the necrotic tumor microemboli from the lungs. Jaffe et al. [8] advocated metabolic or toxic origin, and advise enhanced doses of calcium leucovorine (100 mg every 3 h), while Adam et al. [11] blame it on impurities present in the MTX and recommend analysis of samples of the drug for impurities in cases associated with acute encephalopathy.

Though we did not repeat HDMTX therapy in our patient, other authors have successfully given further cycles of HDMTX without any complication [8, 11]. Anselm et al. [9] have reported a second episode even after reduced dosage of HDMTX (2 g/m²), and they gave subsequent cycles with oral MTX without any further complications.

As most of these patients recover spontaneously within 2–3 days without any specific treatment, there is no definite role for any specific drug to control symptoms. However Bernini et al. [12] and Helene et al. [13] reported the use of Aminophylline in MTX-related neurotoxicity, but their patients also received intrathecal MTX along with an intravenous dose, hence its use in such cases is doubtful.

Conclusions

This report shows that physicians should be aware of the potential CNS complications of HDMTX, which, though transient and without long-term sequelae, may cause considerable anxiety among family members.

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