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Case report

Transient neurological disturbances induced by the chemotherapy of high-dose methotrexate for osteogenic sarcoma

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Temporary neurologic abnormalities were observed in one out of 23 patients undergoing chemotherapy with high-dose methotrexate (HD-MTX) for osteogenic sarcoma. This patient developed sequential symptoms including alternative hemiparesis, dysarthria and altered consciousness 5 days after the second course of HD-MTX (8 gm/m^2 by 6 h continuous infusion) with leucovorin rescue. Laboratory evaluations disclosed normal electrolytes, hemograms and non-toxic serum MTX levels at the onset of the symptoms. Computed tomography of the brain was normal but electroencephalography showed focal theta and delta slow waves over the right temporal-parietal-occipital area. The neurological symptoms resolved completely within 72 h.

Key words: High-dose methotrexate, neurotoxicity, osteogenic sarcoma.

Introduction

Neurotoxicity secondary to methotrexate (MTX) is a major complication of cancer treatment in children and adults.[1] Acute, subacute and chronic encephalopathy have been reported to be associated with intravenous high-dose methotrexate (HD-MTX) therapy (> 5 gm/m^2) in the absence of prior intrathecal MTX administration or cranial ir-radiation.[2–4] Temporary neurologic dysfunction induced by HD-MTX during the therapy of osteogenic sarcoma has been rarely reported previously.[5–8] In this paper, we described a patient with osteogenic sarcoma, who developed a sudden onset but transient neurologic dysfunction 5 days after the administration of HD-MTX (8 gm/m^2) with leucovorin rescue.

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Case report

From January 1988 to September 1993, 23 patients of osteogenic sarcoma with a mean age of 18 years were treated with HD-MTX plus leucovorin rescue at Chang Gung Memorial Hospital. The dosage of HD-MTX ranged from 5 to 12 gm/m^2. The 23 patients received a total of 97 courses of HD-MTX. Only one patient developed neurologic disturbance during his second course treatment.

The patient was a 16 year old boy who developed osteogenic sarcoma in the left distal femur. Past medical history was non-contributory. The extensive work-ups for the tumor, including chest computed tomography (CT) and bone scan, were negative for metastasis. He was initially treated with adriamycin, cisplatin and vincristine at the Veteran General Hospital 1 month previously and then transferred to our hospital for further management. We started chemotherapy with HD-MTX (8 gm/m^2 by 6 h intravenous infusion) plus leucovorin rescue (15 mg intravenously every 3 h for eight doses and then 15 mg every 6 h for another eight doses) weekly. The patient tolerated the scheme well during the first course of HD-MTX; however, 5 days after the second course of the treatment, he experienced sudden onset of right hemiparesis and dysarthria. These symptoms fluctuated but lasted for 48 h and were then followed by left hemiparesis. During the episode, he was intermittently stuporous, agitated and confused. The syndrome gradually disappeared on the third day and he was left with no residua. The treatment consisted of leucovorin 100 mg intravenously every 6 h for 3 days.

Laboratory studies revealed a platelet count of 250 000/mm^3 and a normal electrolytes profile. A

cranial CT scan with contrast enhancement was normal. Cerebral spinal fluid (CSF) examination was not performed. The electroencephalography (EEG) showed focal theta and delta slow waves over the right temporal-parietal-occipital area. The serum levels of MTX were 5.05, 0.39 and 0.11 μM at 24, 48 and 72 h, respectively, after infusion of HD-MTX. These levels were within normal limits. The patient refused further treatment with HD-MTX but he accepted a course of combination chemotherapy with BCD (bleomycin, cyclophosphamide and actinomycin-D) before operation. Since a good response of 80% of the necrotic tumor cells of MTX was reported by pathology, an additional three courses of HD-MTX (8 gm/m^2) with increased leucovorin dose (100 mg every 3 h for eight doses) was given after operation. Fortunately, no further neurologic deficit was observed.

Discussion

MTX, a folic acid antimetabolite, when administered in high intravenous doses of approximately 8–12 g/m^2 body surface area with folinic acid rescue has been shown to be effective in treating osteogenic sarcoma.[9] Due to the advent of more aggressive treatment protocols involving MTX, central nervous system toxicity has become a more pressing issue. Transient neurologic disturbances have been described previously as acute or subacute complications from HD-MTX in the treatment of osteogenic sarcoma.[2–8]

The incidence of neurologic syndrome with MTX treatment was reported as 2.5% by Allen *et al.* (4/158 patients),[3] 5% by Packer *et al.* (2/40 patients)[4] and 15% by Jaffe *et al.* (9/60 patients).[8] The incidence in the current report is 4.3% (1/23 of our patients). The clinical syndrome of acute HD-MTX encephalopathy in humans is characterized by altered sensorium, headaches, aphasia, hemiparesis and seizures.[8] These events occurred as early as a few hours and as late as 20 days after MTX infusion.[8] Cranial CT scan and CSF study usually showed negative findings; however, the EEG was invariably abnormal. No permanent neurologic deficit was encountered in most cases. As described herein, the patient's neurologic signs with hemiparesis and dysarthria fluctuated over a course of 48 h. Cranial CT scan was normal, but EEG showed abnormal slow waves. The neurologic deficit gradually cleared 1 day later.

The mechanism of the reversible neurologic disturbances is not fully determined. A vascular etiology was the explanation offered by Allen *et al.* They had proposed that the reversible neurologic disturbances were caused by an embolic origin from a pulmonary metastasis undergoing lysis.[3] However, Jaffe *et al.* suggested that a metabolic disturbance associated with dihydrofolate reductase might be responsible for the neurologic disturbances induced by MTX.[8] MTX might also impede glucose metabolism or neurotransmitter synthesis.[1,10–13] Nevertheless, there was no evidence of lung metastasis in our patient.

The number of MTX courses administered before the neurologic disturbances reported by Jaffe *et al.* ranged from two to 40.[8] Most of the cases developed neurologic deficit after several courses (two to 11) of treatment. Fritsch *et al.* suggested that MTX could be accumulated in the body tissue.[7] However, elevated MTX levels were neither detected in Jaffe's patients nor in our patient. The pathogenesis of HD-MTX induced transient neurologic disturbance is probably multifactorial. Intravenous HD-MTX administered to rats produced behavior changes, EEG slowing and a profound depression of cerebral glucose metabolism in the absence of systemic organ toxicity. These effects were not obvious when the animals were given adequate leucovorin.[12,13] No further neurotoxicity was found when increased leucovorin rescue doses were administered to our patient during the post-operative HD-MTX treatment.

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