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Clinical Observations

Review of Dextromethorphan Administration in 18 Patients With Subacute Methotrexate Central Nervous System Toxicity

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ABSTRACT

BACKGROUND: The pathogenesis of methotrexate central nervous system toxicity is multifactorial, but it is likely related to central nervous system folate homeostasis. The use of folinate rescue has been described to decrease toxicity in patients who had received intrathecal methotrexate. It has also been described in previous studies that there is an elevated level of homocysteine in plasma and cerebrospinal fluid of patients who had received intrathecal methotrexate. Homocysteine is an *N*-methyl-D-aspartate receptor agonist. The use of dextromethorphan, noncompetitive *N*-methyl-D-aspartate receptor receptor antagonist, has been used in the treatment of sudden onset of neurological dysfunction associated with methotrexate toxicity. It remains unclear whether the dextromethorphan impacted the speed of recovery, and its use remains controversial. This study reviews the use of dextromethorphan in the setting of subacute methotrexate central nervous system toxicity. **METHODS:** Charts of 18 patients who had sudden onset of neurological impairments after receiving methotrexate and were treated with dextromethorphan were reviewed. **RESULT:** The use of dextromethorphan in most of our patients resulted in symptomatic improvement. In this patient population, earlier administration of dextromethorphan resulted in faster improvement of impairments and led to prevention of recurrence of seizure activity induced by methotrexate central nervous system toxicity. **CONCLUSIONS:** Our study provides support for the use of dextromethorphan in patients with subacute methotrexate central nervous system toxicity.

Keywords: methotrexate CNS toxicity, dextromethorphan, homocysteine, NMDA receptor

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Introduction

Methotrexate is a folic acid antagonist; it blocks the synthesis of purines and pyrimidines by inhibiting several key enzymes. A well-known and clinically important side effect of methotrexate is its associated central nervous system (CNS) toxicity, which presents most frequently after intrathecal methotrexate administration; however, it can be observed after intravenous methotrexate at low and high doses. The CNS toxicity has been categorized as being acute, subacute, or chronic.[1] Acute CNS toxicity occurs within a few hours after methotrexate administration, and patients usually exhibit signs of chemical meningitis: somnolence, confusion, headache, nausea, vomiting, and dizziness. Subacute CNS toxicity is observed within days to weeks of methotrexate therapy, and a patient may exhibit seizures or stroke-like signs including hemiparesis, hemisensory deficits, aphasia, dysarthria, dysphagia, and diplopia. Chronic CNS toxicity occurs months to years after methotrexate therapy, and patients exhibit signs of cognitive dysfunction, behavioral abnormalities, and spasticity.[1]

A possible mechanism of methotrexate CNS toxicity is through methotrexate's disruption of remethylation of homocysteine to methionine. Homocysteine is directly toxic to vascular endothelium, and its metabolites are excitatory agonists of *N*-methyl-D-aspartate (NMDA) receptors.[2] Here, we will review cases of 18 patients with subacute

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TABLE 1.
Clinical Features and Details of Therapy of 18 Patients With Subacute Methotrexate CNS Toxicity

S.No	Dx	Patient's Protocol	Age (yr)	Sex	Time Since Last MTX (days)	Dose of MTX	Physical Examination Findings
Group A							
1	ALL	CCG 1961	14	M	12	12 mg IT	Convulsions followed by slurred speech
2	ALL	AALL02P2	3.5	M	6	12 mg IT	Confusion
3	ALL	CCG 1961	15	F	4	12 mg IT	Right sided weakness, dysarthria, expressive dysphagia, and incontinence
4	ALL	CCG 1961	18	F	4	12 mg IT	Confusion, slurred speech, obsessive compulsive behavior, and rumination.
5	ALL	CCG 1991	8	F	4	12 mg IT	Slurred speech, drooling, difficulty moving left arm, difficulty with word finding, ataxia, agitation and complaint of dizziness, and headaches
6	VWD ALL	CCG 1961	5.5	M	3	12 mg IT	Ataxia, dysmetria with right lower extremity weakness and emotional labiality
7	ALL	CCG 1961	14	F	7	12 mg IT	Mental status changes, decrease alertness, slurred speech, left facial droop, inability to speak, and right-sided weakness
8	ALL	AALL02P2	15	M	7	5 g/m^2 IV	Slurred speech and left-sided weakness
9	ALL	CCG 1922	6	F	5	12 mg IT	Right limb and face weakness
10	OS	AOST0791	14	F	2	12 g/m^2 IV	Waxing and waning sensorium and mild dysmetria
Group B							
11	ALL	CCG 1961	6	M	8	12 mg IT	Seizure, disconjugate gaze, ataxia, clumsiness, and cognitive slowing
12	ALL	AALL0232	16	M	3	7.5 mg IT	Right hemiparesis, aphasia, and facial droop
13	ALL	AALL0232	17	M	8	15 mg IT	Mental status changes and left-sided hemiparesis
14	ALL	AALL0232	10	F	7	15 mg IT	Left facial numbness and left arm and leg weakness and numbness
15	ALL	CCG 1961	13	M	3	12 mg IT	Seizure
16	ALL	CCG 1991	2	M	3	8 mg IT	Lower extremity trembling and unsteady gait
17	ALL	CCG 1961	10	F	3	12 mg IT	Disorientation and acute right-sided weakness
18	ALL	CCG 1961	15	F	9	12 mg IT	Difficulty swallowing, talking, right hemiparesis, and increase in agitation with eventual somnolence and aphasia

Abbreviations:
ALL = Acute lymphoblastic leukemia
Ara C = Cytarabine
b.i.d = Twice a day
CNS = Central nervous system
DM = Dextromethorphan
Dx = Diagnosis
F = Female
HC = Hydrocortisone
IT = Intrathecal
M = Male
MTX = Methotrexate
OS = Osteogenic sarcoma
PPx = Prophylaxis
q.d = Once a day
VWD = Von Willebrand Disease
* Resolved = Resolved before DM administration

methotrexate CNS toxicity treated with dextromethorphan at different time intervals after start of their dysfunction.

Patients and Methods

The charts of 18 patients, at various time points of treatment protocol, who had sudden onset of neurological impairments after receiving methotrexate from 2000 to 2012 and were treated with dextromethorphan were reviewed (Table 1). None of the patients had any prior cranial radiation therapy. The dose of dextromethorphan ranged from 1 to 3 mg/kg per day. No adverse reactions to dextromethorphan were noted. Parents and patients were provided information about dextromethorphan and the reasoning behind its off-label use.

The mean age of patients reviewed was 11.2 years. Twelve of 18 patients were noted to be Hispanic based on their own reporting. Most patients (17/18) had the diagnosis of acute lymphoblastic leukemia. All the patients had imaging studies done at the time of presentation that ruled out other intracranial processes, such as hemorrhage, ischemia, masses, or thrombosis, which could have explained their impairments. Neurological deficits noted in the patients ranged from seizure activity to unresponsiveness. The mean time from receiving methotrexate to development of neurological deficit was 5.4 days. Eight of 18 patients started dextromethorphan $\geq$24 hours after start of their findings, titled group A. The remaining 10 patients (group B) received their first dose of dextromethorphan on average within 7.6 hours after start of their findings. One of the 10 patients in group B, Patient 9, had resolution of impairments before receiving dextromethorphan. After dextromethorphan administration, he did not have any recurrence of his impairments. The remaining nine patients in group B improved within 3.5 hours of receiving dextromethorphan. The average response time for group A patients who received dextromethorphan 24 hours or later after start of impairments was 13.9 hours.

Patients 1 and 15 presented with seizure activity without fever or other etiologies for seizure. The seizure of Patient 1 lasted 2 minutes. After his seizure, he was noted to have slurred speech. He was started on dextromethorphan about an hour after start of his seizure activity and development of slurred speech. His slurred speech was noted to improve within about 12 minutes after start of dextromethorphan administration and resolved after 2 hours. He also did not suffer any recurrence of

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