CORRESPONDENCE

Early CNS toxicity after intrathecal methotrexate

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Dear Editor,

Central nervous system (CNS) being a sanctuary site, intrathecal methotrexate (IT MTX) has become a cornerstone for CNS prophylaxis for acute lymphoblastic leukemia. Recently we noticed eight pediatric patients developing transient neurological event following IT MTX. All of them were acute lymphoblastic leukemia (ALL) patients. Four were high risk patients and others were standard risk (based on total count and age). All of them received BFM 86 protocol. Seven were females. Their age ranged from 4–14 years and the median age was 11.5 years. All the patients had normal CSF studies. Five of them received IT MTX along with intravenous high dose MTX (HDMTX) 5 gm/m² before the event. Two received cytosine arabinoside (Ara-C), (75 mg/m² for 4 days) with IT MTX on day one. Only one received cranial irradiation before the event. All the patients developed the event between Day 11 to D14 of IT MTX. Seven patients had hemiparesis and one had quadriplegia. The neurological event recovered within 24 hours in seven of them and within 72 hours on the others. Cerebrospinal fluid (CSF) study was normal in all patients. All of them were exposed to multiple doses of IT MTX prior to the event. Preservative free MTX recommended dosage (12 mg) was used for all patients and proper administration technique under sterile precautions was ensured. Imaging studies were

Age	Sex	Prior IT MTX	Dose of other Rx	Diagnosis
4	F	4	HDMTX 5g/m ²	ALL
8	F	5	HDMTX 5g/m ²	ALL
9	F	2	Ara C 75 mg/m ²	ALL
13	F	7	Ara C 75 mg/m ²	ALL
13	M	4	HDMTX 5g/m ²	ALL
14	F	5	HDMTX 5g/m ²	ALL
10	F	4	HDMTX 5 g/m ²	ALL
14	F	2	Ara C 75mg/m ²	ALL

conducted in all patients within 24 hours of the onset of the event and all had normal standard MR imaging study of the brain. The imaging studies were not repeated later.

The incidence of various neurological events following IT-MTX is estimated around 4–15% [1]. Three distinct clinical patterns of neurotoxicity have been observed (a) an acute toxicity, occurring within hours of IT chemotherapy, probably resulting from chemical arachnoiditis; (b) sub acute toxicity occurring within days or weeks, and characterized by symptoms of seizures, transient paresis, or cerebellar abnormalities; and (c) a delayed leukoencephalopathy form that is more commonly observed when IT MTX is used with cranial irradiation [1].

The mechanism of methotrexate induced neurotoxicity is poorly understood. Both high-dose intravenous MTX and intrathecal MTX are proposed to have association with demyelination, white matter necrosis, loss of oligodendroglia, axonal swelling, microcystic encephalomalacia, and atrophy relatively selective for the deep cerebral white matter [2]. An altered myelin metabolism disturbance induced by

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MTX [3] or elevated levels of homocysteine and its excitatory amino acid neurotransmitter metabolites (homocysteic acid and cysteine sulfinic acid) may mediate, in part, methotrexate-associated neurotoxicity [4]. The absence of significant imaging abnormalities has raised the possibility of cytotoxic edema.

Though high dose intravenous methotrexate and intravenous cytosine arabinoside have been independently associated with neurological events like transient paralysis, the temporal relation of onset of neurodeficits with IT MTX gave the clue in our patients.

Few facts were interesting in our patients. Only paediatric ALL patients developed this peculiar toxicity, none being reported in adult ALL or non-Hodkin's lymphomas (NHL) patients receiving intrathecal methotrexate. There was definite sex predilection for this event, with females being more affected. Interestingly the toxicity is seen around Day 11 to Day 14. Despite the event, we continued IT MTX in all these patients, but no recurrences were noted. Despite such a dramatic event the the standard MR imaging studies were normal in our patients. Fisher et al. analyzed six patients with subacute neurotoxicity due to methotrexate [5]. They reported that initial standard MR imaging

was normal in all patients but diffusion weighted imaging (DWI) showed restriction in deep white matter. The follow up scan in five patients showed abnormal T2W images in the same areas as early as 4 days after the onset of deficit.

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