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HIGH DOSE METHOTREXATE ASSOCIATED WITH POLYNEUROPATHY IN ADULT WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: CASE REPORT

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ABSTRACT

Methotrexate (MTX) is an anti-metabolite that is commonly used in the treatment of several hematologic malignancies. We reports a case of Polyneuropathy associated with high dose MTX administration in an adult with Primary Central Nervous System Lymphoma (PCNSL). A 39- year-old male was started on high dose MTX (8 gm/m^2) following his diagnosis with localized PCNSL .Post third cycle, the patient started losing strength over his right leg. This was followed by bilateral lower limb weakness with hyporeflexia. All laboratory investigations were normal. Naranjo scale was used to assess adverse drug reaction causality. The Patient was referred to the neurologist for further investigations, in which he was diagnosed with sensory motor polyneuropathy predominantly axonal neuropathy in the right lower limb associated with MTX. After discontinuation of MTX, the patient`s physical function improved and he was kept on thiamine 100 mg (IV) three times daily and Neurobion supplements (Vitamin B1= 100 mg+ B6 =200mg + B12 =200mcg) 1 tablet twice daily. With the use of more aggressive treatment regimens in patients with PCNSL, toxicities related to chemotherapy is expected to be increased. Therefore, patients on high doses MTX should be carefully monitored for any neurological toxicity.

Keywords: Methotrexate, Polyneuropathy, PCNS, Lymphoma

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive type of non Hodgkin lymphomas arising in the brain, spinal cord, eyes, and meninges. [1] For decades, radiotherapy was the mainstay of treatment for patients with PCNSL. However, with the addition of chemotherapy; patients` survival has been improved significantly, as evident in several studies and chemotherapy became a crucial part in the course of treatment. [2-4]

Chemotherapy regimens that include methotrexate (MTX) have been used for several years in treating patients with PCNS, because of the drug ability to cross the blood-brain barrier, therefore reaching the involved meningeal sites. [4, 5]

MTX is an anti-metabolite that exerts its effect by inhibiting folic acid synthesis and interfering with DNA synthesis, as well as cells reproduction.[6]To achieve therapeutic concentrations of MTX in the brain, it should be administered intravenously and in high doses (3.5 g/m^2 – 8 g/ m^2).[4-6] Conversely, the use of high doses is associated with the risk of systemic toxicities, such as seizures, transient neurological deficits and encephalopathy.[3,5]The most common neurotoxicities reported in literature are generally related to the intrathecal administration of MTX and mainly are acute or sub-acute toxicities.[5,7] Nevertheless, only few reports highlighted the association of MTX with neuropathy incidences in children. [6, 7]For the aforementioned reasons, we report a case of polyneuropathy associated with high dose MTX administration in an adult with PCNSL.

CASE REPORT:

A 39-year-oldmale, with no chronic illness was diagnosed with primary CNS diffuse large B cell lymphoma (PCNSL) inJuly, 2013 at the National Center for Cancer Care and Research when he presented with dysphasia and left hemiparesis. The staging workup confirmed localized CNS disease with no metastatic lesions and his case was discussed in the lymphoma multidisciplinary team (MDT)meeting, which decided to start him on high dose MTX (8 gm/m^2) through intravenous infusion (IV) and Rituximab 375 mg/m^2every two weeks for 6 cycles.(Table1) The patient received the first cycle of MTX after receiving appropriate urinary alkalization with sodium bicarbonate to ensure that urine PH is greater than or equal to 7. Strict fluid balance intake and output with pH testing was completed every 4-6 hours. In addition, the patient received adequate antiemetic according to the hospital antiemetic protocol. MTX was administered by IV infusion over the course of 4 hours and serum MTX levels were obtained 24 hours after the end of infusion and repeated daily until the level was less than 0.05mcmol/L.Furthermore, the patient received folinic acid 25 mg/m^2 every 6 hours intravenously and then he was shifted to oral folinic acid, when the MTX level was less than0.05 mcmol/L.The patient was also kept on dexamethasone 2 mg orally two times daily to decrease his cerebral edema. The patient tolerated the chemotherapy without clinical and laboratory deterioration and he was discharged on dexamethasone 2 mg orally twice daily and ranitidine 150 mg orally twice daily.

Following the third cycle, the patient started losing strength over his right leg. This was followed by bilateral lower limb weakness and hyporeflexia with 2/5 score in the muscle strength scale. All laboratory investigations were normal, including MTX level; CBC; chemistry; serum folate; proteins levels; cholesterol panel; thyroid panel and vitamin b12 levels. The patient case was referred to neurologist for further investigations.

Cycle	**Chemotherapy Regimen**		**Date**
	Day 1	**Day 3**	
Cycle I	Methotrexate 8 gm/m2 (IV) over 4 hours	Rituximab 375 mg/m2(IV) over 90 minutes	Aug 26, 2013
Cycle II	Methotrexate 8 gm/m2 (IV) over 4 hours	Rituximab 375 mg/m2(IV) over 90 minutes	Sep 18, 2013
Cycle III	Methotrexate 8 gm/m2(IV) over 4 hours	Rituximab 375 mg/m2 (IV) over 90 minutes	Oct 2, 2013

Table (1):Patient`s chemotherapy regimen for 3 cycles

Neurology Assessment:

Motor and sensory nerve conduction velocity as well as F-Wave studies of the right tibial, peroneal, median, ulnar and sural nerves showed the following findings that confirmed evidences of sensory motor polyneuropathy predominantly axonal neuropathy in the right lower limb.

The motor nerve conduction of the right tibial nerve showed delayed distal latency with the low amplitude and within normal limits of the conduction velocity; while it showed low amplitude within normal limits of the conduction velocity and distal latency for the right peroneal nerve. The sensory nerve conduction of the right sural nerve showed reduced conduction velocity with within normal limits of onset latency and amplitude.

For the F-waves studies, the right tibial and peroneal nerves showed mild delayed responses; the right median and ulnar nerves showed normal responses; the motor and sensory nerve conduction of the right median and ulnar nerves showed within normal limits of the distal latencies, conduction velocities and amplitudes.

Based on these findings; The neurologist recommended to stop MTX and to start the patient on thiamine 100 mg (IV) three times daily and Neurobion supplements (Vitamin B1= 100 mg+ B6 =200mg + B12 =200mcg) 1 tablet twice daily. Significant improvement in the patients` function was observed and the patient was able to function normally after 10 days.

Causality Assessment:

Several assessment scales are available to assess adverse drug reaction causality.The Naranjo scale is a valid evaluation tool, which uses 10 assessment points to evaluate the probability of a drug-induced cause. [9] The Scale consists of 10 questions and the total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less. The total score obtained was 7 in our patient's case.

Table (2): Naranjo causality scale for adverse drug reactions

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a antagonist was administered?	+1	0	0	1
4. Did the adverse reaction reappear when the drug was re administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could have on their ow the reaction?	-1	+2	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the blood detected in the blood (or other fluids) in concentrations kno toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total : 7				

DISCUSSION:

MTX is a widely used chemotherapeutic agent in lymphoma treatment that can cause acute, sub acute, and chronic neurological complications. [4-7] Despite the considerable amount of case reports published regarding MTX induced neurotoxicity, the exact mechanism in which MTX causes different neurotoxicities is still not understood. However, it is proposed that direct toxic effects to the CNS and damaging the neuronal tissue could be the reasons. [10]

Up to our knowledge, this is the first case report published regarding high dose MTX association with polyneuropahty in adults with PCNSL. In our patient, there was a tight relationship between the onset of neuropathy symptoms and the use of MTX which strongly suggests a causative link. This is supported by the documented improvement in neuropathy after withdrawal of MTX while all medications were unchanged.

Whether additional preventive measures should be taken to reduce MTX neurotoxicities is still unknown. Previous reports by Cohen IJ, reported that there was no evidence that higher doses of folinic acid can reduce MTX neurotoxicity. In addition, the author concluded that the safe dose of folinic acid should be defined in terms of the dose of MTX given, since consensus for folinic acid dosing or administration does not exist. [9,10]Therefore, further studies should be conducted to investigate other measures that can reduce the risk of neurotoxicity associated with high dose MTX.

CONCLUSION:

Drug-induced peripheral neuropathy is the most plausible diagnosis in our patients` case based on symptom improvement after drug discontinuation and

lack of other possible causes, such as metabolic abnormalities, and other underlying diseases. With the use of more aggressive treatment regimens in patients with PCNSL, toxicities related to chemotherapy is expected to be increased. Therefore, patients on high doses MTX should be carefully monitored for any neurological toxicity.

Ethical considerations: A waiver of informed consent was obtained from Hamad Medical Research Center (MRC).

Disclosure: None of the authors has any conflict of interest to declare in relation to the subject of this manuscript.

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