Original Article

Methotrexate-induced chemical meningitis in patients with acute lymphoblastic leukemia/lymphoma

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Abstract

Background: Intrathecal methotrexate (ITMTX) is an important component in the treatment as well as prophylaxis of leukemia/lymphoma. ITMTX can cause chemical meningitis characterized by vomiting, headache, and fever lasting 2-5 days with spontaneous resolution of symptoms which differentiates this syndrome from bacterial meningitis. **Objective:** This prospective observational study was carried out to determine incidence of post-ITMTX syndrome in patients receiving prophylactic ITMTX as part of Berlin-Frankfurt-Munster (BFM) protocol. **Materials and Methods:** Patients aged 15-50 years receiving BFM 90 or BFM 95 protocol for acute lymphoblastic leukemia or lymphoblastic lymphoma were followed up for post-ITMTX syndrome, defined as vomiting, headache and fever between 38° and 39°C following ITMTX. **Results:** Thirty-three patients received a total of 297 courses of ITMTX. Of the 297 doses of ITMTX, 20 episodes (6.7%) of post-ITMTX syndrome were observed. The incidence of post-ITMTX syndrome was highest after the second dose of ITMTX (24%). The most common symptom of post-ITMTX syndrome was headache which was seen in 17 (85%) patients. Seventeen (85%) patients had vomiting, 10 (50%) patients had fever, and 4 (20%) patients had backache. Meningeal signs were present in 2 (10%) patients. **Conclusions:** Post-ITMTX syndrome is not uncommon in adult patients receiving prophylactic ITMTX for treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma. Patients develop a toxic syndrome closely mimicking acute bacterial meningitis but spontaneous recovery is seen without any neurological sequelae.

Key Words

ITMTX intrathecal methotrexate, MTX methotrexate, post ITMTX syndrome

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Introduction

Intrathecal methotrexate (ITMTX) has been the cornerstone in the treatment as well as prophylaxis of leukemic meningitis.[1] ITMTX has been used at doses as low as 10 μg/kg to as high as 500 μg/kg. ITMTX may be associated with acute local neurotoxicity and/or systemic toxicity. Neurotoxicity of ITMTX ranges from confusion, disorientation, seizures, aphasia, ataxia, dysarthria, paresis, paralysis, and even death.[2,3] Such severe neurological complications need central nervous system disease (CNS leukemia, brain tumor, or brain metastases) as a prerequisite. However, a toxic syndrome closely resembling acute bacterial meningitis has been described in children receiving prophylactic ITMTX courses.[4] This post-ITMTX syndrome is due to chemical meningitis caused by MTX. It is characterized by vomiting, headache, and fever lasting 2-5 days and spontaneous resolution of symptoms which differentiates this syndrome from bacterial meningitis. However, there are no studies of acute methotrexate meningitis in the adult population. This study was undertaken to describe the incidence of post-ITMTX syndrome in patients of acute lymphoblastic leukemia and lymphoblastic lymphoma receiving prophylactic ITMTX as part of BFM protocol.

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Materials and Methods

This was a prospective observational study carried out to determine incidence of post-ITMTX syndrome in patients receiving prophylactic ITMTX from June 2013 to June 2014. Patients aged 15-50 years receiving Berlin Frankfurt Munster (BFM) 90 or BFM 95 protocol for acute lymphoblastic leukemia or lymphoblastic lymphoma were included in the study. Patients with CNS disease at the time of diagnosis/during treatment, patients receiving triple IT and patients who receive intravenous antibiotics for suspected bacterial meningitis following ITMTX were excluded from the study.

BFM protocol is used for the treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma. BFM protocols rely on ITMTX for CNS prophylaxis (along with high dose intravenous methotrexate). BFM 90 and BFM 95 differ in the doses and schedule of chemotherapeutic agents. However, the administration of ITMTX is similar in both the protocols. Both BFM 90 and BFM 95 protocols have incorporated three doses of ITMTX administered every 14 days during induction phase A-A1-A3 (along with intravenous vincristine, daunomycin, L-asparaginase, and oral prednisolone), two doses during induction phase B (B1 and B2) administered every 14 days (along with intravenous cytarabine, cyclophosphamide, and oral 6 mercaptopurine), four doses during consolidation administered every 14 days, C1-C4 (along with intravenous high dose methotrexate and oral 6 mercaptopurine), and two doses administered during re induction (along with oral thioguanine, intravenous cyclophosphamide, and cytarabine). Patients were followed up till the end of consolidation only. The last two doses of ITMTX given during reinduction were not included for analysis because many patients were lost to follow-up.

All lumbar punctures in the study group were performed without either local or general anesthesia. Commercially available preservative free Methotexate (15 mg/ml) was used in a fixed dose of 12 mg in all patients. Under strict aseptic precautions, lumbar puncture was performed with 21 guage LP needle in lateral position, 2 ml cerebrospinal fluid (CSF) was collected for cytological examination and 12 mg methotrexate was injected. No diluent was used along with MTX.

Post-ITMTX syndrome was defined as vomiting, headache, and fever between 38° and 39°C following ITMTX. Baseline patient information regarding age, gender, diagnosis, treatment protocol were recorded. Following ITMTX, all patients were monitored for symptoms (vomiting, headache, fever, backache, leg pain) and signs (temperature, meningeal signs) of post-ITMTX syndrome every 8 hours. Symptomatic treatment in the form of paracetamol for fever and headache and antiemetics for vomiting was administered. None of these patients were subjected to repeat CSF examination, as a diagnosis of bacterial meningitis was not entertained. Whenever a suspicion of bacterial meningitis was entertained, empirical intravenous antibiotics were started immediately and such patients were excluded from the study.

Table 1: Baseline characteristics of participants

Baseline Characteristics (*n* = 33)	Number (%)
Age in years (mean)	22.51
Male/female	23/10 (2.3)
Diagnosis	
Acute lymphoblastic leukemia (%)	19 (57.5)
Lymphoblastic lymphoma (%)	14 (42.5)
Treatment Protocol	
BFM 90 (%)	23 (69.7)
BFM 95 (%)	10 (30.3)

Results

Thirty-five patients fulfilling the inclusion criteria were enrolled in the study. Two patients were excluded from analysis as they developed CNS disease during the course of treatment. Median duration of follow-up was 141 days ranging from 125 to 152 days. Out of 33 patients, 23 were males and 10 were females. [Table 1] Mean age at presentation was 22.5 years, median age was 20 years (range 16 to 46 years). Nineteen patients had acute lymphoblastic leukemia and 14 had lymphoblastic lymphoma. Twenty-three patients received BFM 90 and ten received BFM 95.

Of the 297 doses of ITMTX, 20 episodes (6.7%) of post-ITMTX syndrome were observed. The incidence of post-ITMTX syndrome was highest after the second dose of ITMTX (24%) [Table 2]. After the second dose, the incidence of post ITMTX ranged from 3 to 9% [Figure 1].

Mean age of patients developing post-ITMTX syndrome was 21.35 years and male:female ratio was 1.5 [Table 3]. Seventeen patients had acute lymphoblastic leukemia and three had lymphoblastic lymphoma. Thirteen patients received BFM 90 and seven received BFM 95. The most common symptom of post-ITMTX syndrome was headache which was seen in 17 (85%) patients. Seventeen (85%) patients had vomiting and four (20%) patients had backache. Ten (50%) patients had fever. Onset of fever following ITMTX was on D1 in two patients, D2 in five patients, and D3 in three patients. The maximum temperature ranged from 100 to 102^0 F and fever lasted for 2 to 4 days in all the patients. Meningeal signs were present in two (10%) patients. Onset of symptoms ranged from 4 hours after ITMTX to maximum of 72 hours. Symptoms resolved with symptomatic treatment in 2 to 6 days.

Discussion

Chemical meningitis is one of the neurological adverse effects of ITMTX.[5] It is characterized by headache, vomiting, nuchal rigidity, kernig's sign, photophobia, delirium, and obtundation. Meningitis was attributed to presence of preservatives like methyl hydroxybenzoate, propyl hydroxybenzoate, and benzyl alcohol. However, even with preservative-free MTX, meningitis continued to occur and is due to MTX *per se*. This syndrome is more common and more severe in those with high CSF MTX level.[6] In patients with overt meningeal leukemia, CSF pathways are impaired which leads to high CSF MTX level and higher incidence of post-ITMTX syndrome. Incidence is much lower in patients without CNS disease due to intact CSF pathways. Incidence of chemical arachnoiditis following

Table 2: Incidence of Post ITMTX syndrome in relation to the number of doses of ITMTX received

Number of ITMTX dose	Dose 1 (A1) (%)	Dose 2 (A2) (%)	Dose 3 (A3) (%)	Dose 4 (B1) (%)	Dose 5 (B2) (%)	Dose 6 (C1) (%)	Dose 7 (C2) (%)	Dose 8 (C3) (%)	Dose 9 (C4) (%)
Post ITMTX syndrome	3/33 (9)	8/33 (24)	1/33 (3)	0/33 (0)	3/33 (9)	2/33 (6)	1/33 (3)	1/33 (3)	1/33 (3)

Table 3: Profile of patients developing Post ITMTX syndrome

Characteristics	Number (%)
Age in years (mean)	21.35
Male/female	12/8 (1.5)
Diagnosis	
Acute lymphoblastic leukemia (%)	17 (85)
Lymphoblastic lymphoma (%)	3 (15)
Treatment Protocol	
BFM 90 (%)	13 (65)
BFM 95 (%)	7 (35)
Symptoms/signs of Post ITMTX syndrome	
Headache (%)	17 (85)
Vomiting (%)	14 (70)
Fever (%)	10 (50)
Backache (%)	4 (20)
Meningeal signs (%)	2 (10)

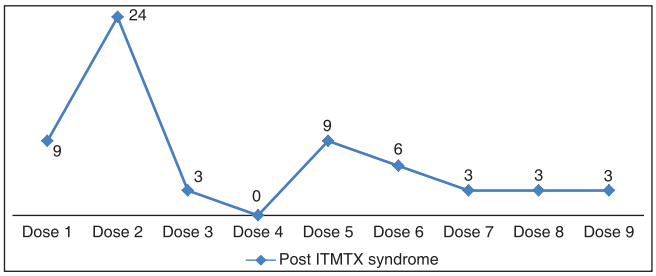

Figure 1: Incidence of Post ITMTX syndrome in relation to the number of doses of ITMTX received

ITMTX (post-ITMTX syndrome) increases with the number of ITMTX and is dose related.[7] Incidence of post ITMTX ranges from 9.8 to 90% in various reports in patients with overt CNS disease and is dose dependent. However, in patients receiving prophylactic ITMTX, incidence of post-ITMTX syndrome is much lower. In a study investigating adverse effects of ITMTX in children with acute leukemia receiving prophylactic ITMTX, 40% patients experienced post-ITMTX syndrome.[4] Data regarding post-ITMTX syndrome in adults is sparse.

When a patient develops a toxic syndrome following ITMTX, it is important to differentiate from acute bacterial meningitis. The CSF changes may range from predominant mononuclear cells and increased protein levels to polymorphonuclear reaction mimicking infectious meningitis. The diagnosis of post-ITMTX syndrome in our patients is substantiated by the following facts. First, the temporal sequence of events that symptoms started 4 to 72 hours following ITMTX. Second, all patients showed a prompt spontaneous recovery with symptomatic treatment without addition of antibiotics. Acute bacterial meningitis would have had a progressive downhill course without antibiotics. Third, by the absence of other symptoms and signs like seizures, altered sensorium, and features of raised intracranial pressure. In a study of characterization of postoperative chemical meningitis after neurological surgery, temperature >40°C and fever lasting more than 7 days were more common in patients with bacterial meningitis compared to chemical meningitis. In the study population, none of the patients had fever >40°C and fever resolved within 4 days of onset in all our patients. In the same study, new onset of seizure disorder, altered sensorium, and focal neurological deficits were seen only in patients with bacterial meningitis.[8]

In none of these patients, CSF examination was attempted. A repeat CSF examination for the purpose of documentation alone would have been unethical from the study point of view. The studies reporting CSF examination findings of post-ITMTX syndrome were done in patients receiving ITMTX once in every 3 days where lumbar puncture was both therapeutic and diagnostic. Patients in our study group received ITMTX every 14 days.

In our study, 20 out of 297 (6.7%) ITMTX patients developed symptoms of meningitis. Incidence much lower compared to earlier reports due to the absence of CNS disease in our patients. In a study by Geiser *et al.*, of adverse effects of prophylactic ITMTX in children with acute leukemia in remission, there was evidence of cumulative methotrexate toxicity.[4] Post-ITMTX syndrome occurred mostly after third and fourth doses and did not recur with longer interval between doses. ITMTX was administered at a dose of 12.5 mg/m2 every 3 to 4 days for a total of five doses. In our patients, such a cumulative toxicity was not seen probably because BFM protocol uses ITMTX once in 14 days and the lower dose of MTX used.

Another observation of our study was that patients with acute lymphoblastic leukemia had a higher incidence of post-ITMTX syndrome compared to patients with lymphoblastic lymphoma, the reason for which is not clear.

The strength of the study is that it has captured a unique pattern of adverse effect of the drug which has been in clinical use for more than 50 years. The limitation of our study is the absence of CSF examination findings including Gram stain and culture. Without CSF findings, it is difficult to differentiate chemical meningitis from bacterial meningitis. However, all our patients had a self limiting illness with spontaneous recovery which is unlikely in bacterial meningitis.

Conclusion

Post-ITMTX syndrome is not uncommon in adult patients receiving prophylactic ITMTX for treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma. Although patients develop a toxic syndrome closely mimicking acute bacterial meningitis, spontaneous recovery is seen without any neurological sequelae.

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