Methotrexate Neurotoxicity in Adult Acute Lymphoblastic Leukemia

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BACKGROUND

- Methotrexate (MTX) neurotoxicity (NT) is a severe acute or subacute central NT with potential long-term neurologic sequelae that is associated with intrathecal (IT) or intravenous (IV) methotrexate.
- MTX NT presents with new, stroke-like focal neurologic deficits, including paresis, paralysis, movement disorders, bilateral weakness, aphasia, dysarthria, altered mental status and/or seizures.[1]
- This adverse event can lead to hospitalizations, treatment modifications and treatment interruptions that can impact efficacy and jeopardize long-term survival.[2]
- The incidence of MTX NT is 3-12% in pediatric ALL series, with some reports of rates as high as 18%. Risk factors in pediatric patients include Hispanic ethnicity, age >10, transaminitis, co-administration with cytarabine or cyclophosphamide, and select genetic polymorphisms.[2-4]
- Limited data exists regarding the incidence of MTX NT in adults, its presentation and clinical features, or its impact on treatment outcomes.
- We aimed to assess the incidence, risk factors for and treatment effects of MTX NT in adult patients with ALL treated at The Mount Sinai Hospital.

METHODS

- We retrospectively reviewed patients with ALL, aged ≥18 years at diagnosis, and treated with regimens containing IV and/or IT MTX at Mount Sinai Hospital from 1/1/2000 - 12/31/2022.
- Patients were defined as having MTX NT if they met the 2016 Ponte di Legno toxicity working group definition of "Methotrexate-related stroke-like syndrome"1 or if they were otherwise deemed to have MTX NT by treating physicians at the time.
- Fisher's exact test was used to assess relationships between patient-factors and MTX toxicity. Overall Survival (OS) was measured using the Kaplan-Meier method.

REFERENCES

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2. Mateos, M.K., et al., Methotrexate-related central neurotoxicity: clinical characteristics, risk factors and genome-wide association study in children treated for acute lymphoblastic leukemia. *Haematologica*, 2021. 107(3): p. 635-643.
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RESULTS

Of 203 patients with ALL included in the analysis, 15 patients (6.9%) developed MTX NT. One of these patients experienced two instances of MTX NT, for a total of 16 events.

There was no statistically significant difference in age (p = .233), sex (p = .791), ALL phenotype (p = .573), Ph-status (p = .583), or presence of CNS leukemia (p = .477) between those who experienced MTX NT and those who did not (**Table 1**).

73.3% of patients who experienced MTX NT were Hispanic, compared to 26.1% who did not experience NT, translating to an odds ratio for neurotoxicity among Hispanic patients of 7.74 (95% CI 2.3564-25.4557, p = 0.0007).

Table 1: Baseline Characteristics

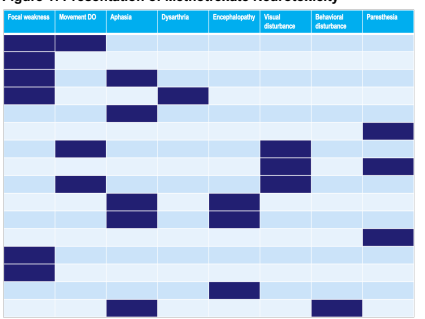
	No NT (*n* = 188)	NT (*n* = 15)
Age, median (range), years	42.5 (18-79)	40.5 (19-62)
Female Sex, % (n)	47.9 (90)	53.3 (8)
Ethnicity, % (n)		
Hispanic	26.1 (49)	73.3 (11)
Non-Hispanic White	26.6 (50)	20 (3)
Black	10.1 (19)	0 (0)
Asian/Pacific Islander	12.2 (23)	1 (6.7)
Unknown/Other	25.0 (47)	0 (0)
ALL phenotype, % (n)		
B-ALL	82.4 (155)	73.3 (11)
T-ALL	16.5 (31)	26.7 (4)
MPAL	1.1 (2)	0 (0)
Ph-status		
Ph-negative	64.9 (122)	20 (3)
Ph-positive	31.4 (59)	73.3 (11)
Ph-like	3.7 (7)	6.7 (1)
Induction Regimen, % (n)		
CALGB 10403/A40501	33.0 (62)	53.3 (8)
Hyper-CVAD	29.8 (56)	20.0 (3)
ECOG 2993	6.9 (13)	0.0 (0)
EWALL-PH-01	6.4 (12)	6.7 (1)
Steroids + TKI	2.1 (4)	0.0 (0)
Unknown/Other	21.8 (41)	20.0 (3)
CNS Leukemia, % (n)	20.2 (34/168)	30.8 (4/13)

RESULTS (CONTINUED)

Symptoms developed after receiving both IT and IV MTX in 4 patients (26.7%), after only IT MTX in 9 (60%), and only IV MTX in 2 (13.3%). NT emerged a median of 8 days (range, 0-14) from IT MTX and 15 days (range 0 - 21) from IV MTX.

Symptoms included unilateral or bilateral weakness (n=6), movement disorder (n=3), aphasia (n=5), dysarthria (n=1), encephalopathy (n=3), visual disturbances (n=3), behavioral disturbance (n=1) and paresthesias (n=3) **(Figure 1)**. No patients experienced seizures during their presentations. Complete (n=12) or partial (n=4) symptom resolution occurred in all patients, with median time to resolution of 2 days (range, 0-13).

Figure 1: Presentation of Methotrexate Neurotoxicity



5/10 patients who had MRI imaging done at the time of the event had new, abnormal findings characteristic of MTX NT. In 2 of these patients the radiographic abnormalities resolved (**Figure 2**).

An equal number of events occurred with administration via LP or via ommaya.

Nine patients were rechallenged with IV and/or IT MTX, with only one NT recurrence.

With a median follow-up of 30 months, there was no difference in OS between patients who experienced NT and those who did not (**Figure 3**).

RESULTS (CONTINUED)

Figure 2: A characteristic rounded, subcortical mass identified in a patient with MTX NT.

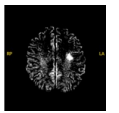
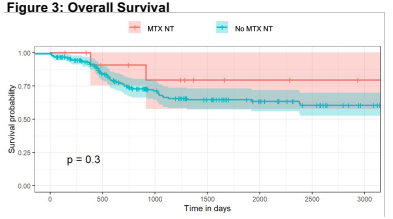


Figure 3: Overall Survival



SUMMARY & CONCLUSIONS

- The incidence of MTX NT in adult ALL is 6.9% and is similar to that in the pediatric population.
- Hispanic race/ethnicity is a significant risk factor.
- This adverse event is more common after IT MTX compared to IV.
- Weakness and aphasia appear to be the most common presenting features, though most patients present with more than one symptom.
- Most symptoms resolve, though a portion of patients have residual neurologic findings.
- Most patients do not experience recurrence on MTX re-challenge.
- Further studies are needed to confirm these results and further clarify the impact of MTX NT on disease outcomes.

CONTACT INFORMATION

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