

[CASE REPORT]

Methotrexate-induced Transient Encephalopathy in an Adolescent and Young Adult Patient with Acute Lymphoblastic Leukemia

Kazuaki Teshima^{1,2}, Masaaki Kume¹, Rui Kondo³, Kenichi Shibata³, Ko Abe^{1,2}, Hiroaki Aono³, Susumu Fushimi³, Satoshi Takahashi⁴, Satsuki Takahashi⁵, Masahiro Saito⁵ and Naoto Takahashi²

Abstract:

A 17-year-old girl was diagnosed with acute lymphoblastic leukemia (ALL). After the administration of high-dose methotrexate (MTX) or intrathecal MTX, the patient experienced transient hemiparesis and motor aphasia. Diffusion-weighted magnetic resonance imaging showed a high-intensity lesion in the bilateral centrum semiovale, and a vasospasm was detected in the proximal segment of bilateral A1 on magnetic resonance angiography. Edaravone was administered, and leucovorin rescue treatment was continued; eventually, the patient's neurological symptoms completely resolved. This finding suggested that vasospasm might be a mechanism underlying MTX-induced transient encephalopathy in adolescent and young adult patients with ALL.

Key words: methotrexate, transient encephalopathy, vasospasm, acute lymphoblastic leukemia, adolescent and young adult

(Intern Med 60: 2115-2118, 2021)

(DOI: 10.2169/internalmedicine.5937-20)

Introduction

Methotrexate (MTX) is an essential drug in the treatment of acute lymphoblastic leukemia. High-dose MTX or intrathecal chemotherapy with MTX is an important central nervous system (CNS) prophylactic treatment for patients with leukemia. MTX-induced encephalopathy occurs in 0.8-15% of patients treated with high-dose MTX (1). The first study related to this subject described the abrupt onset of focal neurological deficits occurring approximately 10 days after chemotherapy with high-dose MTX in children treated for osteogenic sarcoma (2). Encephalopathy can be caused by both intrathecal as well as intravenous MTX (3). These complications have been classified as acute, subacute, or chronic. Subacute encephalopathy generally develops within

5-14 days after treatment with intrathecal or high-dose MTX and resolves within a week without long-term permanent neurological sequelae (4). The pathophysiological mechanism of this syndrome is not well understood. We herein report a case of an adolescent and young adult (AYA) patient with immature B-cell precursor acute lymphoblastic leukemia (ALL) (B-ALL) who presented with transient encephalopathy after receiving intrathecal or high-dose MTX.

Case Report

A 17-year-old girl with a history of epilepsy who presented with a fever and left-sided chest pain was diagnosed with B-ALL. She was treated with combination chemotherapy as induction therapy (consisting of systemic steroids, repetitive intrathecal MTX, vincristine, adriamycin, cyclophos-

¹Department of Hematology, Hiraka General Hospital, Japan, ²Department of Hematology, Nephrology and Rheumatology, Akita University Graduate School of Medicine, Japan, ³Department of Neurosurgery, Hiraka General Hospital, Japan, ⁴Department of Radiology, Hiraka General Hospital, Japan and ⁵Department of Diagnostic Pathology, Hiraka General Hospital, Japan

Received: July 22, 2020; Accepted: November 29, 2020; Advance Publication by J-STAGE: February 1, 2021

Correspondence to Dr. Kazuaki Teshima, green08kazuma@gmail.com

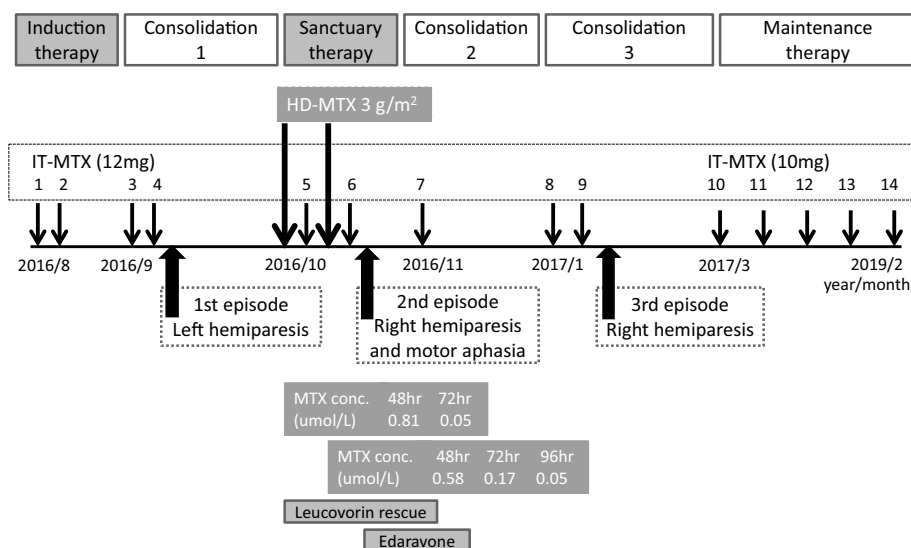


Figure 1. The clinical course of our patient treated with high-dose MTX and intrathecal MTX. Combination chemotherapy consisted of induction, consolidation, sanctuary, and maintenance therapies. High-dose MTX was administered as a sanctuary therapy, and 14 intrathecal MTX injections were administered over the course of treatment. The patient experienced three episodes of neurological deficit in the course of treatment. The plasma concentration of MTX remained normal after treatment with high-dose MTX. Leucovorin rescue and edaravone treatments were administered at the onset of the second episode. MTX: methotrexate

phamide, and L-asparaginase) and achieved complete hematological remission. No CNS involvement was noted at the time of the diagnosis. Following the induction therapy, the patient was treated with consolidation therapy consisting of adriamycin, cyclophosphamide, cytarabine, 6-mercaptopurine, intrathecal MTX, cytarabine, and hydrocortisone. She developed left-sided hemiparesis on the 16th day after receiving the 4th dose of intrathecal MTX (12 mg), cytarabine (30 mg), and hydrocortisone (25 mg) as consolidation therapy (Fig. 1). Computed tomography (CT) of the brain revealed unremarkable findings. She exhibited full, spontaneous neurological recovery within 24 hours. On the 14th day after the administration of high-dose MTX chemotherapy (3 g/m²) as sanctuary therapy, she presented with right hemiparesis and motor aphasia (Fig. 1). A manual muscle test of the biceps and quadriceps femoris was performed and revealed a muscle grade of 2/5. Diffusion-weighted magnetic resonance imaging (DWI-MRI) showed a high-intensity lesion in the left centrum semiovale (Fig. 2a). These findings were only detected on DWI-MRI and were not observed on T2-weighted MRI or fluid-attenuated inversion recovery. Suspecting that stroke or encephalopathy might have occurred, edaravone was administered for 4 days and leucovorin rescue treatment (15 mg per once, 8 times) was continued. Twenty-four hours after the onset of the second episode, a high-intensity lesion in the right centrum semiovale was found on DWI-MRI (Fig. 2b) in addition to the lesion noted in the left centrum semiovale (Fig. 2c). The patient's neurological symptoms completely resolved within 5 days. Follow-up MRI performed a week later showed no signs of abnormalities in these areas (Fig. 2d). During the onset of

the second episode, a vasospasm was detected in the proximal segment of bilateral A1 on magnetic resonance angiography (MRA) (Fig. 2f) compared with a previous finding before the onset of ALL (Fig. 2e). The patient's laboratory results were normal except for the hemoglobin level (8.1 g/dL), which indicated anemia. The plasma concentration of MTX was normal after treatment with high-dose MTX (Fig. 1). The findings of a cerebrospinal fluid analysis were normal. An oligoclonal band was not detected. The patient tested negative for herpes simplex virus 1 and 2, human herpesvirus 6, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, and John Cunningham virus on multiple polymerase chain reaction tests. Although she had a history of epilepsy and had been treated with levetiracetam, no new abnormalities were detected on electroencephalography at the onset of the second episode. Twenty-four hours after the onset of the second episode, the vasospasm in the proximal segment of the right A1 had disappeared, as observed on MRA (Fig. 2g). On the 15th day after the 9th dose of intrathecal MTX (12 mg), cytarabine (30 mg), and hydrocortisone (25 mg), the patient developed right-sided hemiparesis (Fig. 1) but eventually recovered within 24 hours. The dosage of MTX was reduced to 10 mg after the 10th dose of intrathecal MTX. Further reduction in the MTX dosage was thought likely to increase the risk of CNS relapse, so the dosage of MTX was maintained. The administration of another 5 doses of intrathecal MTX (10 mg), cytarabine (30 mg), and hydrocortisone (25 mg) was achieved by reducing the MTX dosage and providing hydration. The patient did not develop neurological complications after receiving the aforementioned treatment. At 16 months after the chemo-

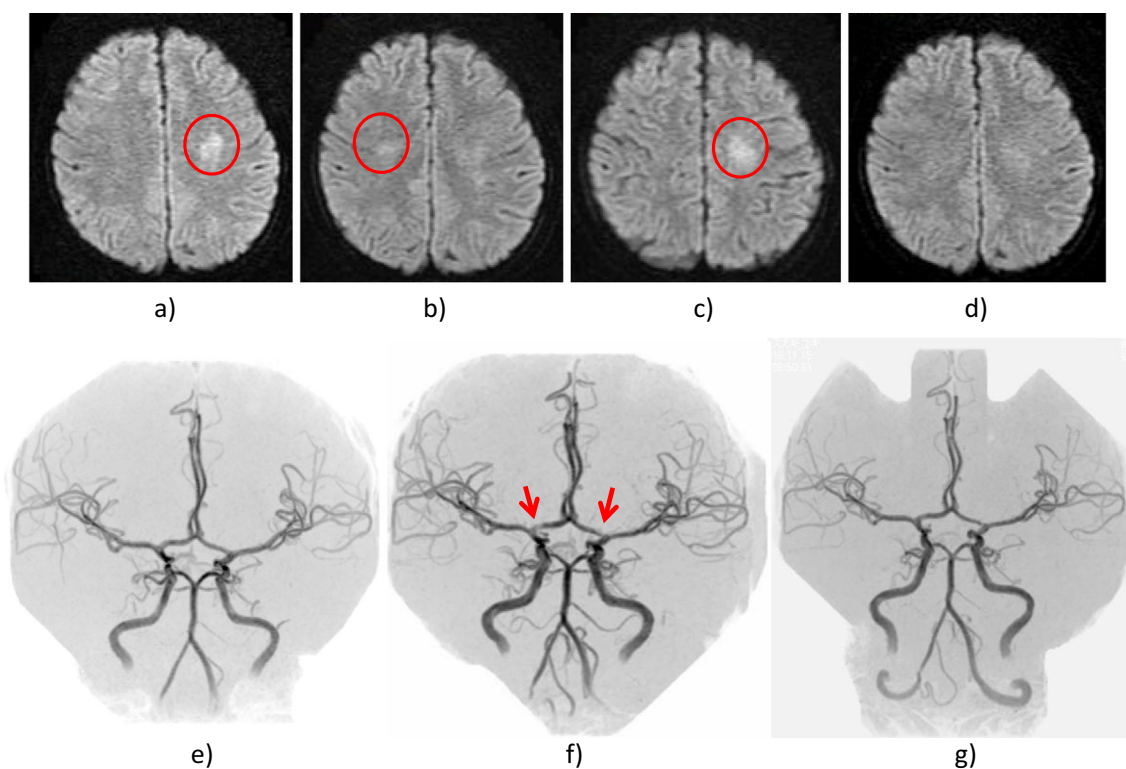


Figure 2. Imaging findings. a) DWI-MRI showed a high-intensity lesion in the left centrum semi-ovale at the onset of the second episode after treatment with high-dose MTX. b) DWI-MRI showed a high-intensity lesion in the right centrum semi-ovale 24 hours after the onset of the second episode. c) DWI-MRI showed high-intensity lesion in the left centrum semi-ovale 24 hours after the onset of the second episode. d) DWI-MRI showed the absence of abnormalities one week after the onset of the second episode. e) MRA showed the absence of stenosis before the onset of ALL. f) MRA revealed a vasospasm (arrows) in the proximal segment of bilateral A1 at the onset of the second episode after treatment with high-dose MTX. g) The vasospasm in the proximal segment of right A1 subsequently disappeared, as observed on MRA 24 hours after the onset of the second episode. DWI-MRI: diffusion-weighted magnetic resonance imaging, MRA: magnetic resonance angiography, ALL: acute lymphoblastic leukemia, MTX: methotrexate

therapy, the patient had not experienced disease recurrence.

Discussion

It is difficult to predict the onset of transient encephalopathy by monitoring the MTX concentration because the pharmacokinetics of MTX are not related to the frequency of episodes (5). Our patient's plasma MTX concentration returned to normal immediately after treatment with high-dose MTX (Fig. 1). Although the etiology of transient encephalopathy has been unclear in most previously reported cases, the proposed pathogenic mechanisms include altered methionine and homocysteine, increased levels of sulfur-containing excitatory amino acids, elevated adenosine levels, and reduced tetrahydrobiopterin levels, all of which may affect multiple neuronal pathways (6, 7).

Stenosis was noted in the proximal segment of bilateral A1 on MRA (Fig. 2f) despite not being detected on MRA two years before the second episode (Fig. 2e). It was restored on the day after the onset of the second episode (Fig. 2g). Therefore, this change was thought to indicate vasospasm.

DWI-MRI is the most common modality used for detecting transient encephalopathy, as conventional CT, T1- or T2-weighted MRI, and MRA fail to show consistent abnormalities that characterize MTX-induced encephalopathy (8, 9). If vasospasms are a characteristic finding of transient encephalopathy, MRA may be useful for its diagnosis. The causal relationship between vasospasm and encephalopathy remains unclear, but one of the possible pathophysiologies is that MTX induces vasogenic edema, resulting in vascular endothelial injuries. These changes induce breakdown of the blood-brain barrier, which in turn results in vasospasm (10, 11).

Most patients tolerate re-challenge treatment, but complications can recur, with a variable reported incidence ranging from 10% to 56% (3, 8, 9, 12). In cases of MTX re-challenge, some studies have suggested that the administration of aminophylline as a prophylactic agent prior to high-dose MTX and leucovorin rescue treatment is effective (13, 14). Another study stated that these neurological complications were not observed after adjusting the dosage and number of intrathecal MTX injections (15). In our case,

the administration of another five doses of intrathecal MTX was achieved by reducing the MTX dosage and prolonging the leucovorin rescue treatment.

High-dose MTX (1.5-8 g/m²) and age >10 years old were associated with an increased risk of transient encephalopathy in children with ALL (16). Rubnitz et al. also reported that an age >10 years old is associated with transient encephalopathy in children with ALL (9). The trend toward a reduced MTX clearance in adolescents may contribute to the age-associated risk, although no significant relationship was observed between the MTX pharmacokinetic parameters and encephalopathy (9). Although transient encephalopathy is common in children with malignancies, it has also been reported in AYA and adult patients. In a recent study, AYA patients were treated with a “children-oriented” regimen with intensified intrathecal MTX and high-dose MTX instead of an “adult-oriented” regimen (17, 18). Such an approach may result in a greater increase in MTX-induced transient encephalopathy in AYA patients than previously reported. MTX-induced transient encephalopathy should be considered as a possible cause of neurological symptoms. MTX-induced transient encephalopathy must be distinguished from stroke and CNS infiltration early for the successful management of this condition. We encountered an AYA patient with B-ALL who developed MTX-induced transient encephalopathy that was thought to have been caused by vasospasm, a potential mechanism underlying the development of MTX-induced transient encephalopathy.

The authors state that they have no Conflict of Interest (COI).

References

- Relling MV, Fairclough D, Ayers D, et al. Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *J Clin Oncol* **12**: 1667-1672, 1994.
- Allen JC, Rosen G, Mehta BM, Horten B. Leukoencephalopathy following high-dose iv methotrexate chemotherapy with leucovorin rescue. *Cancer Treat Rep* **64**: 1261-1273, 1980.
- Cyriac S, Rajendranath R, Sagar TG. Early CNS toxicity after intrathecal methotrexate. *Indian J Hematol Blood Transfus* **24**: 186-187, 2008.
- Endo A, Fuchigami T, Hasegawa M, et al. Posterior reversible encephalopathy syndrome in childhood: report of four cases and review of the literature. *Pediatr Emerg Care* **28**: 153-157, 2012.
- Anselm CW Lee, Li CH, Wong YC. Transient encephalopathy following high-dose methotrexate. *Med Pediatr Oncol* **41**: 101-102, 2003.
- Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. *Chemotherapy* **49**: 92-104, 2003.
- Drachman RA, Cole PD, Golden CB, et al. Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity. *Pediatr Hematol Oncol* **19**: 319-327, 2002.
- Inaba H, Khan RB, Laningham FH, Crew KR, Pui CH, Daw NC. Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric with cancer. *Ann Oncol* **19**: 178-184, 2008.
- Rubnitz JE, Relling MV, Harrison PL, et al. Transient encephalopathy following high-dose methotrexate treatment in childhood acute lymphoblastic leukemia. *Leukemia* **12**: 1176-1181, 1998.
- Lee MJ, Cha J, Choi HA, et al. Blood-brain barrier breakdown in reversible cerebral vasoconstriction syndrome: implications for pathophysiology and diagnosis. *Ann Neurol* **81**: 454-466, 2017.
- Singhal AB. Postpartum angiopathy with reversible posterior leukoencephalopathy. *Arch Neurol* **61**: 411-416, 2004.
- Walker RW, Allen JC, Rosen G, Caparros B. Transient cerebral dysfunction secondary to high-dose methotrexate. *J Clin Oncol* **4**: 1845-1850, 1986.
- Prasanth G, Peush B, Akash S, Parthasarathy S, Tenali S. Methotrexate induced acute encephalopathy-occurrence on rechallenge and response to aminophylline. *Indian J Hematol Blood Transfus* **30**: 105-107, 2014.
- Bernini JC, Fort D, Griener JC, et al. Aminophylline for methotrexate-related neurotoxicity. *Lancet* **345**: 544-547, 1995.
- J Sato, Y Yuasa, H Tanaka, T Ninomiya, M Hirose, M Miyao. Transient cerebral dysfunction induced by VCR, HD-MTX in a child with acute lymphocytic leukemia. *Rinsho Ketsueki* **27**: 2162-2167, 1986.
- Dufourg MN, Landman-Parker J, Auclerc MF, et al. Age and high-dose methotrexate are associated to clinical acute encephalopathy in FRALLE 93 trial for acute lymphoblastic leukemia in children. *Leukemia* **21**: 238-247, 2007.
- Stock W, La M, Stanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. *Blood* **112**: 1646-1654, 2008.
- Rytting ME, Jabbour EJ, O'Brien SM, Kantarjian HM. Acute lymphoblastic leukemia in adolescents and young adults. *Cancer* **123**: 2398-2403, 2017.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).