Annals of Clinical and Medical Case Reports

Case Series

ISSN 2639-8109 | Volume 11

Pharmacokinetics of Methotrexate during Chemotherapy Administration in a Patient with Acute Lymphoblastic Leukemia

Serinelli S, Nasr MR, Elkins M and Cao ZT*

Department of Pathology & Laboratory Medicine, State University of New York, Upstate Medical University, Syracuse, NY, USA

***Corresponding author:**

Zhimin Tim Cao,
Department of Pathology, SUNY Upstate Medical University, Syracuse, NY, 13210, USA

Received: 25 July 2023
Accepted: 29 Aug 2023
Published: 07 Sep 2023
J Short Name: ACMCR

Keywords:

Methotrexate; Acute lymphoblastic leukemia; Intrathecal administration; Therapeutic drug monitoring

Abbreviations:

MTX: methotrexate; IV: intravenously

Citation:

Cao ZT, Pharmacokinetics of Methotrexate during Chemotherapy Administration in a Patient with Acute Lymphoblastic Leukemia. Ann Clin Med Case Rep. 2023; V11(4): 1-4

1. Case Description

A 36-year-old male with a past medical history of Acute Lymphoblastic Leukemia and type 2 diabetes was transferred to the Upstate Medical University Hospital for continuation of chemotherapy. The patient initially presented to a local hospital with epistaxis and was originally treated for immune thrombocytopenic purpura with intravenous immunoglobulins and steroids. The patient denied trauma or a history of bleeding disorder. He subsequently became pancytopenic with poor response to multiple blood transfusions. A bone marrow biopsy was performed and reviewed for consultation at the Upstate Medical University Hospital, which showed a relapse of Acute B Lymphoblastic Leukemia/Lymphoma. The blasts detected by flow cytometry analysis expressed CD10, CD19, CD20, cytoplasmic CD79a, and TdT. BCR-ABL1 was negative by FISH. The patient was subsequently admitted to the Upstate Medical University Hospital and was treated with the chemotherapy regimen R-HYPER-CVAD-MTX-ARA-C, consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate (MTX), and cytarabine for a few treatment cycles.

During the treatment, the patient's primary physician observed that the blood MTX concentrations did not respond or increase as much after two recent administrations (Figure 1, days 6 & 7) as previously observed after MTX administration (Figure 1, day 1 - administration; day 3 - concentration measurement). The physician consulted the Core/Chemistry Laboratory to seek an explanation. An investigation was carried out throughout pre-analytical, analytical and post-analytical phases including the MTX dosage, time and route of administration for each dosing and sampling, type of samples received, sample handling and storage, QC and recent proficiency testing performance, recode of recent calibration and reagent lots, patient renal function, and medications that may interfere with the accuracy of the analysis. No deficiencies or issues were identified in these areas except that the MTX was given intrathecally for the unexpectedly low results of MTX concentrations (Figure 1, days 6 & 7), whereas another dosing was given five days prior via peripheral I.V. (Figure 1, day 1).

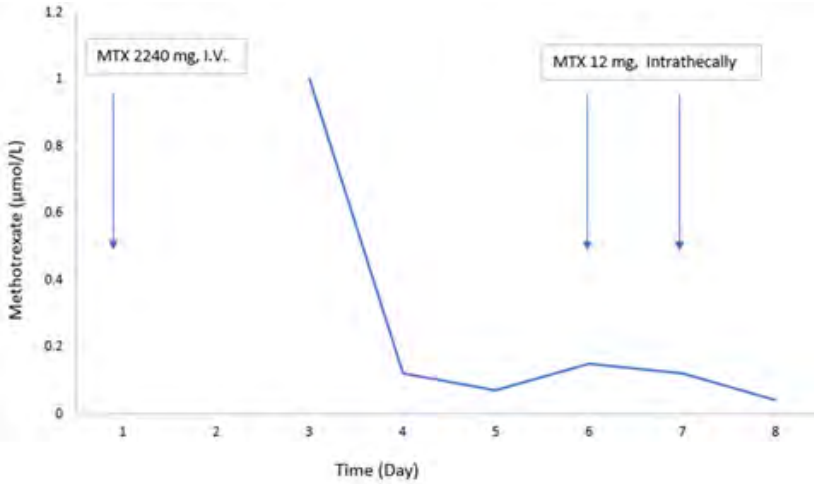

Figure 1: MTX concentrations determined in the lithium heparin plasma samples collected on the various days of the treatment cycle from the patient. The arrows indicate the time of MTX administrations via intravenous (I.V.) and intrathecal routes.

2. Discussion

B-lymphoblastic leukemia/lymphoma is diagnosed by a combination of morphology and immunophenotyping, while further classification is now mainly by defined cytogenetic and/or molecular abnormalities. Approximately 80% of cases occur in children, while the remainder occurs as aggressive disease in adults. Only a minority of patients with Acute Lymphoblastic Leukemia have meningeal disease at the time of initial diagnosis [1]. However, these patients frequently have meningeal leukemia at the time of relapse. Therefore, central nervous system prophylaxis with intrathecal chemotherapy is essential for these subjects [2].

MTX inhibits dihydrofolic acid reductase, is used as a chemotherapeutic agent in the treatment of a variety of diseases including neoplastic diseases, adults with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, systemic lupus erythematosus, and adults with severe psoriasis [3]. Once MTX enters cells via the reduced folate carrier, it becomes the polyglutamated form that inhibits dihydrofolate reductase enzymatic activity resulting in a reduction of dihydrofolates to tetrahydrofolate, therefore reduction of the de novo synthesis of purines and pyrimidines, ultimately inhibiting the DNA synthesis, repair and cellular proliferation [3]. MTX can be administered with high, intermediate, or low doses depending on the nature of treated disorders and the route of administration. MTX can be given via oral, intramuscular, intravenous, intrathecal, or subcutaneous routes [3].

MTX concentrations in serum/plasma samples are measured during treatment with high-dose therapy (>500 mg/m2) as therapeutic drug monitoring to prevent toxicity [3]. Toxicity is indicated if MTX concentration is >10 µmol/L, >1 µmol/L, or >0.1 µmol/L at 24 hours, 48 hours or 72 hours after administration, respectively [4]. MTX toxicity can be due to various causes, e.g., increased patient susceptibility during treatment, and intentional or unintentional overdoses. The most common MTX side effects are associated with tissues with rapid turnover cells, such as gastrointestinal system, e.g., nausea, vomiting, diarrhea, mucositis, stomatitis, esophagitis and elevated hepatic enzymes. Its toxicity can also cause renal failure, rash, myelosuppression (leukopenia, pancytopenia, thrombocytopenia), acute lung injury, tachycardia, hypotension, and neurologic dysfunction (depression, headache, seizures, motor dysfunction, stroke-like symptoms, encephalopathy, coma).

Patients with MTX toxicity can be treated with activated charcoal and/or hemodialysis in the event of a recent oral overdose. Methotrexate with pKa of 5.5 is mainly excreted via kidneys. Managing and maintaining urinary pH in alkaline conditions by adequate hydration and giving sodium bicarbonate can decrease the risks for intratubular precipitation of the drug and obstructive nephropathy during the treatment period [3].

Two antidotes are commonly used together for the treatment of MTX toxicity. Glucarpidase catalyzes the enzymatic reaction that extracellularly converts MTX into diamino-N10-methylpteroic acid (DAMPA) and glutamate, the two nontoxic metabolites, resulting in a removal of extracellular MTX. Leucovorin (folinic acid) intracellularly transforms to tetrahydrofolate despite the presence of MTX, which can resume the formation of purines and pyrimidines, therefore rescuing cells, causing deactivation of intracellular MTX effects [3].

There are many FDA-approved assays used in measuring MTX, e.g., enzyme-multiplied immunoassay technique (EMIT), fluorescence polarization immunoassay (FPIA), capillary electrophoresis (CE) or high-performance liquid chromatography (HPLC) coupled with either a UV, fluorescence, or mass spectrometer detector [5]. In this study, ARK™ Methotrexate Assay (ARK Diagnostics Inc.), a homogeneous immunoassay, was used for measuring MTX concentration in lithium heparin plasma samples of the patient [6]. In the reaction of measurements, MTX in the patient sample competes against MTX-glucose-6-phosphate-dehydrogenase conjugate (MTX-G6PDH) for the anti-MTX antibody. In the absence of MTX, MTX-G6PD binds the antibody which inhibits and keeps

the G6PD enzymatic activity at the basal level. However, in the presence of MTX, the unbound or free fraction of MTX-G6PDH is enzymatically active, and the levels of the MTX-G6PDH activity are proportional to the MTX concentration in the patient sample. The MTX-G6PD converts the coenzyme nicotinamide adenine dinucleotide (NAD) to NADH, as a by-product of the reaction, which is measured spectrophotometrically. The product information of this assay states that the endogenous enzyme does not interfere with the results because the reagent coenzyme NAD works only with the G6PDH enzyme expressed in and purified from bacteria, and the assay is not subject to interference with 7-hydroxymethotrexate, the major metabolite of MTX, and other 16 folate analogs. However, this assay is interfered by DAMPA, the minor MTX metabolite, the concentration of which can be significantly increased in patients receiving glucarpidase as a rescue therapy [6]. Therefore, the ARK Methotrexate assay should not be used for patients treated with glucarpidase within 5-7 days after the termination of the treatment [6]. These possible interferences do not apply to the patient of this study, since we learned that no glucarpidase or other folate analogs were given to the patient, and the original concern was about reduced MTX values, rather than elevated values due to cross reactivity.

After a thorough investigation that excluded all the limitations applicable to the assay, we learned that on day 1 (Figure 1) MTX was given intravenously with a high dose of 2,240 mg in 1 liter of 0.9% saline solution over 24 hours at 41.7 mL/hr. The second and third doses were given intrathecally on day 6 at 11:20 hour and day 7 at 11:11 hour, respectively, with a dose of 12 mg for each administration. The differences in the doses and routes of MTX administration, intravenous vs intrathecal, were determined to be the cause of the discrepancy in the plasma MTX values between days 1 and 6 & 7. Similar observations were also obtained by other studies [7, 8] showing that the plasma MTX levels increased with a much smaller magnitude and decreased with a slower rate when MTX was administered intrathecally than by the I.V. route. When given intrathecally, the duration of maintenance of plasma MTX concentration is increased, acting as a slow-release form of the drug, therefore determining a longer systemic exposure of MTX. Due to the prolonged drug clearance, it is worth noting that MTX toxicity when MTX is administered intrathecally exceeds that by oral or intravenous routes. The delayed MTX clearance can be due to the drug not readily crossing the blood-brain barrier and intracellular polyglutamated MTX needing to be converted to MTX for transport into the extracellular space [3, 8]. MTX toxicity can be exacerbated for patients with renal function impairment and/or the existence of drug-drug interactions. It is suggested that MTX concentration be monitored closely in each cycle of treatment and an extended duration of "rescue" therapy using leucovorin be considered [3, 8, 9].

MTX administration via lumbar puncture or intrathecal has been a commonly employed procedure for chemotherapy in the management of leptomeningeal carcinomatosis. However, rather a large variation in the ventricular MTX concentrations was revealed and the procedure is subject to epidural and subdural leakage (7). Ommaya reservoir, a surgically placed intraventricular catheter allowing repeat drug delivery into the CSF, can be an alternative and showed potential pharmacokinetic benefits of delivering chemotherapy in pediatric patients. An Ommaya reservoir can especially become useful in patients with obesity, prior lumbar surgery or anatomic limitations where Lumber Puncture is difficulty to perform [2, 10, 11].

3. Conclusion

We demonstrated and clinicians should be aware that a much lower level of plasma MTX concentration increase after intrathecal administration than intravenous administration of MTX. Interpretation of MTX test results should be given in conjunction not only with clinical information, but also with the dosage and route of drug administration, and results from other applicable diagnostic procedures when appropriate.

References

1. Duffield AS, Mullighan CG, Borowitz MJ. International Consensus Classification of acute lymphoblastic leukemia/lymphoma. Virchows Arch. 2023; 482: 11-26.
2. Wilson R, Osborne C, Halsey C. The Use of Ommaya Reservoirs to Deliver Central Nervous System-Directed Chemotherapy in Childhood Acute Lymphoblastic Leukaemia. Paediatr Drugs. 2018; 20: 293-301.
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/011719s131lbl.pdf
4. Milone MC, Shaw LM. Therapeutic Drugs and Their Management – Methotrexate. In: Rifai N, Horvath AR, Wittwer C., eds. Tietz textbook of clinical chemistry and molecular diagnostic. 6th ed. St. Louis, Missouri: Elsevier. 2018; p800-31.
5. Karami F, Ranjbar S, Ghasemi Y, Negahdaripour M. Analytical methodologies for determination of methotrexate and its metabolites in pharmaceutical, biological and environmental samples. J Pharm Anal. 2019; 9(6): 373-91.
6. https://www.ark-tdm.com/products/cancer/methotrexate/pdfs/ARK_Methotrexate_Assay_Rev07_August_2017.pdf (Accessed December 2022)
7. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N Engl J Med. 1975; 293: 161-6.
8. Jacobs SA, Bleyer WA, Chabner BA, Johns DG. Letter: Altered plasma pharmacokinetics of methotrexate administered intrathecally. Lancet. 1975; 1(7904): 465-6.
9. Abelson HT, Fosburg MT, Beardsley GP, Goorin AM, Gorka C, Link M, Link D. Methotrexate-induced renal impairment: clinical studies and rescue from systemic toxicity with high-dose leucovorin and thymidine. J Clin Oncol. 1983; 1(3): 208-16.

10. de Oca Delgado MM, Díaz BC, Zambrano JS, Juárez VG, Martínez MSL, Martínez EC, et al. The Comparative Treatment of Intraventricular Chemotherapy by Ommaya Reservoir vs. Lumbar Puncture in Patients With Leptomeningeal Carcinomatosis. Front. Oncol. 2018; 8: 509.
11. Kopmar NE, Cassaday RD. How I prevent and treat central nervous system disease in adults with acute lymphoblastic leukemia. Blood. 2023; 141: 1379-88.