HEMOADSORPTION WITH HA 230 ADSORBER IN CASE OF ACUTE DELAYED METHOTREXATE CLEARANCE IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA AFTER HIGH-DOSE CHEMOTHERAPY

Vitaliy Sazonov[a,b], Askhat Saparov[b], Zaure Tobylbayeva[b], Bolatbek Jubaniyazov[b], Samat Issakov[b], Abduzhappar Gaipov[c]*

[a]Department of Biomedical Sciences, Nazarbayev University School of Medicine, Nur-Sultan, Kazakhstan; [b]Pediatric Anesthesiology and Intensive care Unit. "University Medical Center" National Research Center for Maternal and Child Health, Nur-Sultan, Kazakhstan; [c]Department of Clinical Sciences, Nazarbayev University School of Medicine, Nur-Sultan, Kazakhstan

ABSTRACT

Background. High dose methotrexate (HDMTX) is very likely to cause a number of side effects and manifest itself as hepatotoxicity, nephrotoxicity, mucositis, and neurotoxicity. A several studies demonstrated the efficacy of extracorporeal detoxification methods such as plasma exchange, hemodialysis, hemodialysis filtration, and hemoperfusion for the treatment of MTX delayed clearance. However, none of the existing methods as effective as expected and limited for general implementation due to procedure related complications. **Material and Methods**. Here we report a successful implementation of HA-230 hemoadsorption procedure to remove cumulated MTX from the body and reduce its toxicity in a child with acute lymphocytic leukemia (AAL) after high-dose chemotherapy. **Results and Conclusion**. Based on our results, single hemoadsorption procedure with the HA-230 adsorber in case of delayed methotrexate clearance was safe and well-tolerated in a pediatric patient with ALL and would significantly improve the patient's condition. Further studies needs to demonstrate its safety and efficacy in a large number of pediatric patients

INTRODUCTION

HDMTX has proven an effect and still playing a significant role in the treatment of different type malignances in children, including ALL, non-Hodgkin lymphoma, osteosarcoma and others [1]. However HDMTX is very likely to cause a number of side effects and manifest itself as hepatotoxicity, nephrotoxicity, mucositis, and neurotoxicity. MTX is eliminated by renal excretion involving passive glomerular filtration and active tubular reabsorption and secretion [2].
A number of studies have been published demonstrating the use of extracorporeal detoxification methods for the treatment of MTX delayed clearance: plasma exchange (PE), hemodialysis (HD), hemodialysis filtration (HDF), and hemoperfusion (HP) using an activated carbon absorption column [3]. However, for various reasons, none of the methods is universally safe and effective.

MATERIAL AND METHODS

An eight-year child (weight – 18 kg, S- 0.79m2) was admitted to the department of hematology with the diagnosis of ALL FabL2, T – IV type, high risk group, neuroleukemia. Taking into account clinical and laboratory data, HDMTX (in a dose of 5 grams per m2) was started. Later on, according to the protocol, the patient was receiving intravenous hydration, leucovorin rescue. However, conservative treatment had resulted in no positive change in patient condition and the child has developed acute kidney injury in combination with delayed methotrexate clearance, which was reason to transfer patient in to the intensive care unit (ICU).
Acute kidney injury led to the initiation of pediatric (continuous veno-venous hemodiafiltration) CVVHDF with the "Prismaflex" device (Baxter, US). As a part of pilot study with obtained approval from the Clinical Research Ethics Committee of "University Medical Center" (No. 5, June 30, 2020) and signed informed consent by parents. The HA-230 adsorber (Jafron, Zhuhai City, China) was initiated and maintained for the next 4 hours. The HA-230 adsorber was installed after the hemofilter. During the four hours procedure, the blood samples were collected from the extracorporeal circuit at the following time points: after 5 minute of initiation (0h), two hours later (2h) and just before the timing of procedure (4h). Blood sampling was done on three different points of the system. The first point (P1) – before the filter, second point (P2) – between the filter and adsorber, and the last one (P3) – after the adsorber HA-230. A single procedure of CVVHDF combined with HA-230 adsorption resulted in reduction of methotrexate level from 540.7 to 79.60 µmol/l immediately (reduction rate is -85.27%) during the four hours (Table 1). The MTX level was 49.04 µmol/l 12 hours after the procedure. Later the patient received leucovorin and hydration (after the acute kidney injury was resolved) and after 24 hours, the MTX level reached 28.32 µmol/l. The patient was transferred from ICU to the hematological unit and 48 hours after the procedure the level of methotrexate reduced to 14.60 µmol/l. The routine blood biochemistry and hematologic parameters improved as well clinical condition

Table 1. Methotrexate levels obtained from different points of combined CVVHDF-Hemoadsorbsion system during the procedure.

The time of sampling	Point 1 (before dialyzer-filter)	Point 2 (between dialyzer-filter and HA-230 adsorber)	% of reduction between P1 and P2	Point 3 (after HA-230 adsorber)	% of reduction between P2 and P3	% of reduction between P1 and P3
0h	540.70 µmol/l	522.34 µmol/l	-3.39%	415.22 µmol/l	-20.5 %	-23.21
2h	199.43 µmol/l	191.62 µmol/l	- 3.91%	142.03 µmol/l	-25.8%	-28.78
4h	86.52 µmol/l	83.82 µmol/l	-3.12%	79.60 µmol/l	-5.03	-7.99
Reduction rate from 0h point-1 to 4h point-3 (from 540.7 to 79.6 µmol/l)						-85.27%

DISCUSSION

To the best of our knowledge, this is a first successful implementation of HA-230 adsorber to remove blood methotrexate level and to reduce its toxicity due to delayed elimination in a pediatric patient with AAL after high dose chemotherapy. A single four hours procedure of HA-230 adsorption coupled to CVVHDF significantly reduced the blood methotrexate level for 85.27%. A few existing methods allowing the eliminating of MTX from the body and reducing the toxic effects have been reported in the literature. Fujikura, E., et al describe four cases and each of them uses one of the existing methods [3]. Hemodialysis allowed achieving a reduction rate of 58.3% ±6.17. And this method is one of the available ones. However, it has a number of known side effects as well as limitations to conduct hemodialysis in a low weight pediatric patients. Hemodiafiltration is another option; however, limited removal rate (40.0 ± 5.63%) may also require continuous and repeated procedure. The combination of hemodialysis and hemoperfusion is probably one of the most promising and has made it possible to achieve the rate of reduction 57.9 ±10.6% [3]. A combined hemodialysis and plasma exchange have also demonstrated the 45.7±14.7% removal rate of MTX level [4]. However, this method requires a large amount of donor plasma transfusion, which undoubtedly increases the risk of infection.

CONCLUSION

Timely detection of an increase in methotrexate levels and initiation of treatment will avoid serious, sometimes irreversible, consequences. Management of methotrexate toxicity using the HA-230 adsorber in case of delayed methotrexate clearance showed 85.27% reduction rate during the single 4 hours procedure and well tolerated in a pediatric patient with ALL. Further studies needs to demonstrate its safety and efficacy in a large number of pediatric patients.cc

Acknowledgement
The authors express their special gratitude to all those involved in the treatment and care of the patient in this difficult time: parents, doctors, nurses, and clinic staff.

References
1. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232. J Clin Oncol. 2016 Jul 10;34(20):2380-8
2. Joerger M, Huitema AD, van den Bongard HJ, et al. Determinants of the elimination of methotrexate and 7-hydroxy-methotrexate following high-dose infusional therapy to cancer patients. Br J Clin Pharmacol. 2006 Jul;62(1):71-80
3. Fujikura E, Akiu M, Miyauchi K, et al. Blood purification therapies in methotrexate-induced acute kidney injury: four case reports. Renal Replacement Therapy. 2017;3(1).
4. Kitamura M, Kitamura S, Fujioka M, et al. Methotrexate-induced acute kidney injury in patients with hematological malignancies: three case reports with literature review. Renal Replacement Therapy. 2018 2018/10/03;4(1):39.