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

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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, hemodiafiltration, 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 to improve 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 AAL and would significantly improve the patient’s condition. Further studies need 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 malignancies 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), hemodiafiltration (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, neureleukemia. Taking into account clinical and laboratory data, HDMTX (in a dose of 5 grams per m2) was started. Later, based on 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 venovenous hemofiltration) CVVHD 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, Zhaluhi 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 minutes (Point 1), 2 hours later (Point 2), 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-Hemoadsorption system during the procedure.

<table>
<thead>
<tr>
<th>The time of sampling</th>
<th>Point 1 (before filter)</th>
<th>Point 2 (between filter and HA-230 adsorber)</th>
<th>% of reduction between P1 and P2</th>
<th>Point 3 (after HA-230 adsorber)</th>
<th>% of reduction between P2 and P3</th>
<th>% of reduction between P1 and P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0h</td>
<td>540.70 μmol/l</td>
<td>522.54 μmol/l</td>
<td>-3.39%</td>
<td>415.22 μmol/l</td>
<td>-20.5 %</td>
<td>-23.21%</td>
</tr>
<tr>
<td>2h</td>
<td>199.44 μmol/l</td>
<td>191.62 μmol/l</td>
<td>-3.91%</td>
<td>142.03 μmol/l</td>
<td>-25.8%</td>
<td>-28.78%</td>
</tr>
<tr>
<td>4h</td>
<td>86.32 μmol/l</td>
<td>83.12 μmol/l</td>
<td>-3.12%</td>
<td>79.60 μmol/l</td>
<td>-5.03%</td>
<td>-7.99%</td>
</tr>
<tr>
<td>Reduction rate from 0h to 4h point: 1 to 4h point -3 (from 540.70 to 79.60 μmol/l) -85.27%</td>
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</table>

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% ± 17. And this method is one of the available ones. However, it has a number of known side effects as well as limitation in a pediatric patient with AAL after high dose chemotherapy. Hemodialfiltration is another option; however, limited removal rate (40.1 ± 5.63%) may also require continuous and repeated procedure. The combination of hemodialysis and hemoperfusion is probably one of the most promising and has many reversible 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.

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.