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How to rescue high-dose methotrexate induced nephrotoxicity and literature review about hemodiafiltration?

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Abstract: Methotrexate (MTX) is a highly renal and liver toxicity drug used in hematological malignancy treatment in children and adults. High-dose methotrexate (HD-MTX) therapy may cause impairment of kidney and decrease the elimination of MTX, at the same time, the serum concentration of MTX increased. Today the treatment for preventing MTX toxicity after renal shutdown is Carboxypeptidase. We report a patient who experienced nephrotoxicity after the HD-MTX infusions during the treatment for non-Hodgkin lymphoma (NHL) and received hemodiafiltration (HDF) with large dose of leucovorin (LV) to treat MTX intoxication. LV is very potent in the prevention of neurotoxicity and administration of LV could protect the normal cells, but the dosage and duration of LV should be according to the MTX concentration. Although a large dose of LV was applied, the patient's condition did not improve. It was found that the HDF with large dose of LV to save the patient and steadily improved the patient's clinical condition.

Keywords: High-dose methotrexate, leucovorin, hemodiafiltration, pharmacists, nephrotoxicity.

INTRODUCTION

Methotrexate (MTX) is especially important in the treatment of the adult and pediatric cancers, including acute leukemia NHL and osteogenic sarcoma (Stoller *et al*., 1977; Mitchell *et al*., 1968; Abrey *et al*., 1998). MTX is brought by poor selectivity, inevitably interfering with the normal cell's metabolism, especially the HDMTX chemotherapy (3-5gMTX/m^2), Also, the adequate hydration, folinic acid, and alkalized urine still can appear with the different degrees of adverse reactions, while acute kidney injury (AKI) can develop in 2% to 12% of the patients (Widemann *et al*., 2018). MTX and its metabolites precipitate within the renal tubule and develop into crystal nephropathy which causes nephrotoxicity, The AKI impairs the MTX clearance, leading to the toxic concentrations accumulate and the risk for additional adverse events increasing (Perazella and Moeckel 2010).To prevent the MTX's adverse effects, the plasma concentration should be continuously monitored or 36h after the MTX infusion, while LV should be administered. The HD-MTX with LV rescue has been used as a therapeutic strategy in oncology for more than a decade (Ackland and Schilsky 2010).

The purpose of serum MTX concentration monitoring is to notify the clinicians the possibility of developing drug toxicity and adjust the LV rescue therapy (Borsi *et al*., 1990).

The levels of MTX >20μmol/L after 24h administration, >2μmol/L after 48h administration and >0.2μmol/L after 72h administration are associated with higher toxicity (Widemann and Adamson 2006). When the MTX concentrations reached 100μM, even the 10-fold higher LV concentrations (1,000μM) could not protect the bone marrow cells from toxicity (Pinedo *et al*., 1976). One approach used to reduce the plasma MTX concentrations and the related toxicity of the prolonged MTX exposure intermittent hemodialysis with or without LV rescue (Pinedo *et al*., 1976). Nevertheless hemodialysis is known to be ineffective, an extensive literature review showed that HDF may be effective in the extremely severe cases. The continuous monitoring and timely intervention effective accelerate MTX excretion, prevent the occurrence of toxicity and allow patients to receive subsequent chemotherapy treatments (Stoller *et al*., 1977; Perazella and Moeckel., 2010).

By analyzing the patient who had MTX metabolic delay with HDF and large dose of LV rescue, his treatment outcome is successful. The recent literatures about the HDF guidelines were discussed in this article.

MATERIALS AND METHODS

A 20-year-old man (weighing 54.5kg, BSA 1.70m^2) had been diagnosed with non-Hodgkin lymphoma (NHL) for two months. The HDMTX (3g/m^2) was being prepared to administer through intravenous (IV) infusion for 24h with vigorous IV hydration and urine alkalinization. About 12h after starting the MTX infusion, the patient complained of discomfort with edema and oliguria (urine volume only 400ml), and experienced nephrotoxicity. The physicians

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considered the AKI caused by MTX and discontinued further MTX to quick-check renal function and MTX concentration. The serum MTX concentration was analyzed by the Chemiluminesent Micropaticle Immuno Assay. Also, the 12h serum concentration after infusion was 148.7μM. Meanwhile, the serum creatinine concentration had risen from 76μmol/L to 169μmol/L. With continue IV hydration, the urine output remained appropriately high and pH of urinary remained between 7 and 8. In general, an elevation of the serum creatinine concentration exceed more than 50% over the baseline is defined as AKI, the toxic MTX concentration and the AKI occurred.

RESULTS

Based on the MTX serum concentration and serum creatinine concentration, the clinical pharmacists advised clinician to stop right away the chemotherapy process and with the MTX concentrations should take large dose of LV to rescue. Through consulting relevant literature, the clinical pharmacists recommend LV 150mg micro pump q3h or 300mg micro pump q6h, the clinician eventually take LV 150mg micro pump q3h and alkalized urine through sodium bicarbonate tablets 0.9g po q3h and hydrotalcite tablets 500mg po q3h. But the MTX concentration at 24h was 82μM (toxic range >20μM), 49.5umol/L at 36h, the serum creatinine concentration was 300μmol/L at that time. Regarding the MTX concentration and serum creatinine, the decline was not obvious. The clinicians started HDF treatment base on the MTX characteristics 36h after the MTX infusion. After 10 times of HDF, the HFD was stopped 276h after the MTX infusion and the MTX concentration declined to 1.06μmol with the serum creatinine was 272μmol/L. There was no oral mucositis, liver injury, or other side effects 444h after the MTX infusion. The MTX concentration has declined to 0.5μmol with the serum creatinine of 195μmol/L. Also, the patient's urine output returned to normal (urine volume 3750ml) (fig. 1). The patient was then continuing chemotherapy regime without MTX and his kidney function parameters remain within the normal ranges.

INVESTIGATIONS

LV rescue dosage

Based on the related references on the continually elevation of serum MTX concentrations at 24h (>5-10μM), 48h (>1.0μM), and 72h (>0.1μM) after the administration of MTX, they were predicting the occurrence of toxicity (Widemann and Adamson 2006). MTX micro precipitation in the renal tubules was common and led to kidney injury with delayed MTX excretion and oral mucositis (Wiczer *et al*.,2016). The patient who received HD-MTX therapy showed delayed MTX elimination and suffering from AKI. The administration of LV after HD-MTX treatment was essential to prevent the severe side effects (Joannon *et al*., 2004). The LV rescue has been a footstone of HD-MTX treatment for more than 30 years. Also, In the treatment of children with acute lymphocytic leukemia (ALL) (Joannon *et al*., 1984), where MTX has been used in a dose ranging from 1g/m^2 to 33.6g/m^2, the LV could effectively neutralized the MTX effects.

HDF literature review

Hemopurification includes hemodialysis, Peritoneal dialysis, hemodiafiltration, High-flux hemodialysis, plasma exchange and so on. Dialysis-related technology can be held in a relatively short period of time effectively to reduce the MTX concentration. But the therapeutic effect of each technology is controversial. Based on the relevant literature, contrast the characteristics of each type of blood purification are as follows (table 1). We found that by use of HDF generated the greatest decrease in

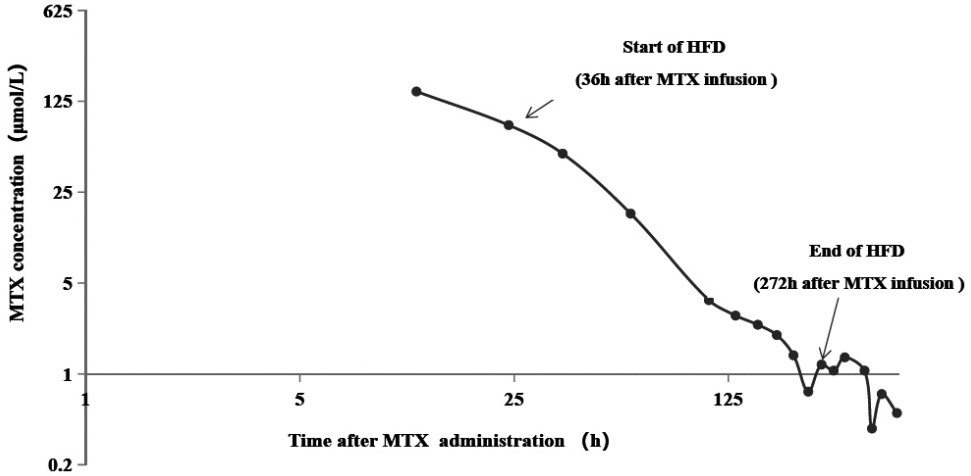

Fig. 1: Changes in serum creatinine and plasma methotrexate concentrations relative to the patient.

Table 1: Efficacy of Methotrexate Removal Methods[a]

Methods	No. of patients reported	MTX (μM) (range)		MTX Decrease (%)	Post procedure MTX rebound increase
		Preprocedure	Postprocedure		
Hemodialysis	13	1.0(0.01-511)	0.8 (0.008-206)	50(3-90)	<20% of postprocedure to 100% of preprocedure levels (2 patients)
HDF	4	2.0(0.19-90.0)	0.45(0.1-2.0)	82(44-98)	25-43% of postprocedure levels
HFD	9	71.9(1.45-18.13)	42.0(2.5-293.0)	75.5(42.0-94.0)	≥50% of postprocedure level
Peritoneal dialysis	2	1.77(0.53-3.0)	Minimal decrease	Minimal Decrease	—
Plasma exchange	10	3.8 (0.12-32.0)	2.3 (0.12-37.0)	26 (0-72)	20% of postprocedure levels (3 patients)

a: Widemann BC1, Balis FM, Kempf-Bielack B, *et al*. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. Cancer 2004; 100(10):2222-2232. MTX: methotrexate; HDF: Hemodiafiltration; HFD: High-flux hemodialysis. The median values for plasma methotrexate concentrations preprocedure and postprocedure, % decrease in methotrexate concentration.

MTX concentrations (median, 82%; range, 44-98%) with 25-43% MTX rebound increase of Post procedure, while use of high-flux hemodialysis resulted in the decrease in plasma MTX concentrations (median, 75.7%; range, 42–94%) with ≥50% MTX rebound increase of post-procedure level.

Some methods are known regarding MTX removal by hemodiafiltration(HDF). HDF uses convection and diffusion in the treatment of MTX intoxication, it is combination of the two methods of molecules' removal. HDF dialyzer aperture is thinner than any ordinary dialysis membrane. Using ultra filtration can increase the removal of the solute. *In vitro* and *in vivo* experiments confirmed that hemodialysis can effectively remove MTX through blood dialysis where the MTX half-life was significantly reduced in the body (Sauer *et al*., 1990). When the MTX blood concentration is high, the hemodialysis has a better curative effect, reducing the biological MTX half-life, which may be one of the reasons that is related to the huge difference in the curative effect of hemodialysis (Cecyn *et al*., 2003; Djerassi *et al*., 1977). Peritoneal dialysis lead to a lowest decrease in plasma MTX concentrations alone (Saland *et al*., 2002). Plasma exchange eliminates the toxic substances in the plasma of the patients' bodies, while replacing the same amount of fluid to the patient. But the MTX clearance rate could be related to the concentration of the plasma MTX. The lower the concentration of MTX results in reduced removal efficiency (Saland *et al*., 2002). Hemodialysis patients can correct electrolyte disorder, while plasma exchange and hemoperfusion may not be able to achieve this purpose.

The MTX consists of small molecules which is a weak acid with a molecular weight of 454Da, MTX is combined to serum albumin with variable protein binding, combined with plasma albumin rate at about 50% and does not change with serum concentration, insoluble in water and with MTX substance of similar molecular weight has the efficient clearance, making the dialysis efficiency high. Also, in the conventional therapy way, dialysis-based methods have limited effectiveness used in remove MTX, while in the serious cases, HDF may be effective.

TREATMENT

The LV dosage or regimen was according to the concentration of MTX which is time-dependent medicine (Ackland and Schilsky 2010). Meanwhile, combining the FDA online provide two copies of the injectable LV specifications for the patient rescue dose, respectively, which are 150mg q3h and 75mg q3h ivgtt. After a comprehensive consideration, clinical pharmacists suggested LV 150mg q3h or 300mg q6h ivgtt and was accepted by the physician. The clinical doctors eventually adopted the LV at 150mg q3h. Although a large dose of LV was applied, the patient's condition did not improve. After reading lots of literature and careful consideration, clinical doctors chosen the HDF with large dose of LV to save the patient, the patient's clinical condition steadily improved.

DISCUSSION

There are a large number of publications described different methods that attempt to solve the potential problem about the reason of delay elimination of MTX which could provide a way to cure the patients with renal injury (table 1). These therapeutic methods reveal that in eliminating MTX have limited effectiveness.

This case highlights the rapid and effective clearance of plasma MTX using HDF in a patient diagnosed with NHL and HDF with a high substitution volume. It is an effective mode of rapid MTX clearance among patients with toxic levels and renal impairment. HDF can not only correct the patients with electrolyte disorder, but also increase the plasma MTX efficiency in the choice of a single dialysis treatment of MTX poisoning and conditional hospital priority in use. Many reports found that hemoperfusion, combined with hemodialysis or HDF, than any kind of dialysis technology alone can effectively remove MTX (Reiss *et al*., 2016). The study found that using a single blood purification therapy in patients with MTX blood concentrations declined to about 52% (26% to 82%) (Widemann and Adamson 2006).

The serum MTX concentrations of this patient for 228h and 252h after the infusion process were 0.73μmol/L and 1.18μmol/L, respectively. After 252h, the HDF has stopped. The serum MTX concentrations of 276h, 300h after infusion had 1.06μmol/L and 1.34μmol/L, respectively. The patient appeared twice in the concentration of recoil phenomenon. The MTX levels rebound was caused by MTX tissue-blood redistribution. The use of dialysis-related treatment showed the presence of MTX in the body. The concentrations that are more prone to bounce, but unrelated with the MTX plasma concentration, needed the dialysis to effectively reduce the MTX plasma concentration. Plasma MTX concentration after dialysis was rebound and was between 10% and 221% of post-procedure MTX concentration, the percentage of pre-procedure MTX level was between 90% and 100% (Widemann and Adamson 2006). Also, this patient with pericardial effusion and left pleural effusion, the MTX fluid could distribute into the third space, such as ascites and pleural effusions can actually change MTX pharmacokinetics (Ziółkowska *et al*., 2013). Both lead to bounce blood drug concentrations.

Some patients applied the systematical measurements couldn't achieved the MTX concentration and were much higher than recommended (Chabner and Chabner 1973). If patients were exposed to MTX concentrations under 0.01μmol and 0.05μmol as long as 24h could lead to myelosuppression and gastrointestinal toxicity, separately (Howard *et al*., 2016). By using hyper hydration, urine alkalization and LV rescue, HD-MTX could be safely applied to the patients with normal renal function. The patients with the normal renal function given administered dose remained 80%-90% unchanged in the urine in 48h. According to current guidelines, the dose of LV should be adjusted according to serum MTX levels to prevent its adverse effects. The reversal of MTX by LV is competitive. When the MTX concentration increases, the higher concentrations of LV are required. MTX is mainly removed by kidney, renal injury caused delay of MTX excretion, MTX concentration continuous elevation result in LV rescue of no avail and MTX relevant toxicities occurred. The reason of nephrotoxicity caused by HDMTX was that MTX and its metabolites precipitate within the renal tubules (Widemann *et al*., 2004). The adverse reactions of MTX are related to the concentration and have exposure to the toxic concentration time (Ackland and Schilsky 2010). During MTX poisoning, the patient should immediately take effective treatment to reduce the blood drug concentration of MTX in the shortest time. Until now, for treat the MTX intoxication, clinicians have been attempted different patterns of dialysis-based methods. According to the above analysis, the most efficient method of extracorporeal removal is HDF. This was capabled of 75.7% (42-94%) of MTX excretion (Widemann *et al*., 2004) within 3h to 5h. The purpose of this guideline therapy was to guide the patients experienced delayed elimination of MTX with nephrotoxicity. The patients with renal dysfunction should be given urinary alkalinization and hydration with bicarbonate, at the same time, LV should be administered every 6h with high dose for patients undergo HDF. To prevent underlying fatal danger, the HDF should be start as soon as possible without hesitation for the patients with renal injury or experiencing MTX intoxication. All these interventions need carry out without delay to restrain further toxic effects and promote renal function recovery, when patients recovered their renal function, they could continue HD-MTX therapy. The clinical pharmacists participate in the treatment of the patients to get better care. Also, they are an indispensable personnel of the clinical treatment team.

CONCLUSION

Therapeutic drug monitoring should be initiated 12-24 h post methotrexate (MTX) infusion. HDF is an effective mode of rapid clearance of MTX in patients with renal impairment. Active involvement into the treatment and evaluation of the effects on the patient reflected the advantage and importance of the multidisciplinary cooperation when complex diseases are experienced.

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