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Case Report
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Effective Rescue of High Dose Methotrexate-Induced Acute Kidney Injury Using Combined Extracorporeal Modalities in a Patient with Osteosarcoma

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Abstract

Background: High-Dose Methotrexate (HDMTX) based therapy has been used for the treatment of osteosarcoma. HDMTX is generally well tolerated with pre-treatment hydration, urinary alkalinization and leucovorin rescue. There are few reports of successful treatment of extremely high serum MTX concentration induced toxicities.

Case Details: The present study presents the case of a 21-year-old female with newly diagnosed osteosarcoma, who received her first neoadjuvant chemotherapy with HDMTX (12 gm/m^2), which was complicated by acute kidney injury, stomatitis and myelosuppression. At 24 h after the MTX infusion, her serum MTX level was extremely high at >1,000 μmol/L. She received diclofenac 25 mg three times daily for 8 days and trimethoprim-sulfamethoxazole for one day prior to the use of HDMTX. Her renal function recovered completely after 8 sessions of combined high flux hemodialysis and hemoperfusion followed by high-dose continuous venovenous hemodiafiltration and high-dose leucovorin.

Discussion: Concomitant use of trimethoprim-sulfamethoxazole and non-steroidal anti-inflammatory drugs potentially reduces the excretion of MTX and therefore increases the risk of HDMTX toxicity. Based on these results, the authors support the efficacy of combined modalities, such as high flux hemodialysis combined with hemoperfusion, followed by continuous hemodiafiltration in dealing with acute kidney injury secondary to HDMTX.

Keywords: Methotrexate; Acute Kidney Injury; Extracorporeal Therapy

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Introduction

Methotrexate (MTX) is a folic acid antagonist, which is administered at high doses in combination with cisplatin, carboplatin and ifosfamide for the treatment of osteosarcoma. High dose MTX (HDMTX) is usually administered over 4 h to 6 h to obtain peak values >1,000 mol/L, which are considered sufficient for positive treatment effects [1,2]. When MTX is administered at high doses, patients should receive aggressive pre- and post-treatment with intravenous hydration and urinary alkalinization to prevent adverse effects [3]. High blood levels of MTX are generally well tolerated for a short period. However, toxicity can occur after persistent exposure to high or low levels of MTX. Therefore, leucovorin rescue is typically administered intravenously 24 h after the initiation of MTX treatment, until the serum concentration of MTX falls to 0.05 μmol/L. Patients are at high risk of developing toxicity if their blood concentration of MTX is ≥ 10, ≥ 1 or ≥ 0.1 μmol/L at 24, 48 and 72 h after administration, respectively [4,5]. The main toxic effects of MTX are bone marrow suppression, oral mucositis, elevated liver enzymes and Acute Kidney Injury (AKI). Diligent monitoring of plasma MTX concentrations can enable the timely recognition of the delay of MTX elimination and toxicity.

MTX is metabolized in the liver and eliminated *via* the kidneys. Despite this, AKI develops in 2% to 12% of patients, resulting in delayed drug elimination and elevated plasma MTX levels [6]. At present, various extracorporeal techniques are used to remove excessive MTX, including high flux Intermittent Hemodialysis (IHD), plasma exchange and Hemoperfusion (HP) using an

activated carbon absorption column and continuous hemofiltration [7-12]. MTX has moderate (50%) plasma protein binding and a large volume of distribution (0.76 L/kg). Combined treatment with IHD and HP would theoretically produce excellent elimination, as it would remove both free and protein-bound MTX. Unfortunately, even when high flux IHD is effective, post-dialysis rebounds in serum MTX concentrations of 10% to 220%, particularly following shorter dialysis sessions have been reported [6]. Therefore, continuous removal of MTX by continuous renal replacement therapy is required to maintain lower MTX serum levels. To the best of our knowledge, the current study is the first to report on the successful treatment of AKI due to MTX toxicity, using the combined modalities of high flux IHD, HP and continuous renal replacement therapy.

Case Presentation

A 21-year-old female (body surface area 1.36 m^2) with newly diagnosed osteosarcoma over her left proximal tibia, received her first course of neoadjuvant chemotherapy with high dose MTX according to the Taiwan Pediatric Oncology Group 2017 osteosarcoma protocol. On admission, the patient had normal liver function; Aspartate Aminotransferase (AST), 24 IU/L; Alanine Aminotransferase (ALT), 18 IU/L; alkaline phosphatase, 1,652 IU/L; lactic dehydrogenase, 788 IU/L with an initial Blood Urea Nitrogen (BUN) and creatinine level of 13 mg/dL and 0.5 mg/dL, respectively.

She received diclofenac 25 mg three times daily and oxycodone 10 mg 1# QD for 8 days before HDMTX to relieve her severe malignant bone pain. Pneumocystis jirovecii pneumonia prophylaxis with Trimethoprim-Sulfamethoxazole (TMP-SMX) 80/400 mg daily was initiated one day before HDMTX. For prechemotherapy hydration, she received 5% dextrose 0.33% saline with 10 MEq potassium and 33.2 MEq $NaHCO_3$ at 125 mL/h. After receiving hydration for 2 h and achieving a urine pH of >7, 12 gm/m^2 HDMTX (total 16 gm) was administered by infusion over 4 h. IV hydration was continued and her urine pH was maintained at >7.0 after HDMTX treatment.

At 4 h post-HDMTX infusion, her creatinine rose to 1.25 mg/dL with a normal urine output. However, the urine output gradually decreased thereafter. At 24 h after the infusion, renal function tests revealed a BUN of 52 mg/dL and a serum creatinine of 2.98 mg/dL, which resulted in a serum MTX concentration of 1,327 mol/L. Liver enzymes were slightly elevated with an ALT of 55 U/L. The leucovorin rescue dose was amended to 200 mg intravenously every 3 h. Forty-one hours after the initiation of HDMTX, the blood tests revealed a creatinine level of 4.38 mg/dL, BUN 63 mg/dL (the BUN/creatinine ratio was 14.4), uric acid 9.5 mg/dL, ALT 69 IU/L, and mild hyperkalemia with a serum potassium of 4.6 mEq/L. The MTX level remained >1,500 mol/L. A urine analysis reported microscopic hematuria (RBC: 10-19/HPF), proteinuria 30 mg/dL and no evidence of crystals or active sediment. A renal ultrasound demonstrated no evidence of nephrolithiasis or hydronephrosis.

These test results suggested that MTX toxicity was the main etiology of the AKI. Her intravenous leucovorin was further increased to 1,000 mg/m^2 every 3 h. Potential drug interactions between HDMTX and TMP-SMX or diclofenac were identified so these two drugs were soon replaced by dapsone and oxycodone, respectively. To facilitate MTX clearance as well as management of the emerging AKI, combined high flux IHD and HP were performed for 6 h to enable faster removal of MTX. For the combined IHD and HP, the connection between IHD and HP was in series and the charcoal adsorption column (Absorba 300; Gambro, Hechingen, Germany) was connected after the dialyzer (FX 80, Fresenius). Blood flow and dialysate flow rates in IHD were 150 ml/min and 500 ml/min, respectively.

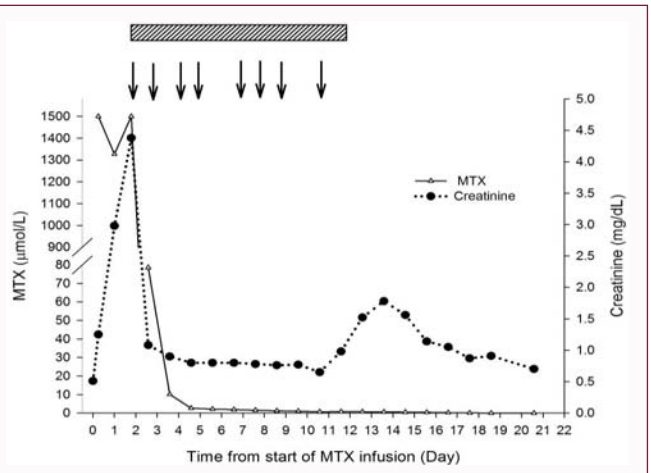

Figure 1: Serum MTX concentrations and creatinine following HDMTX infusion. Time 0 indicates the start of the 4-hour HDMTX infusion. The arrows indicate the combined high-flux IHD and HP sessions. The bar indicates CVVHDF.

Table 1: Efficacy of MTX removal by combined high flux IHD and HP for 6 hours.

Post MTX infusion (days)	Number of treatment session	Serum MTX level (μmol/L) Pre IHD+HP	Post IHD+HP	MTX reduction rate (%)
2	1st	>1,500	243.66	*83.8
2.75	2nd	48.23	16.16	66.5
4.08	3rd	7.05	3.34	52.6
4.83	4th	3.43	1.73	49.6
7	5th	1.46	1.46	0
7.75	6th	1.56	1.03	34
8.83	7th	1.22	0.85	30.32
10.75	8th	0.65	0.66	0

Abbreviations: HP: Hemoperfusion; IHD: Intermittent Hemodialysis; MTX: Methotrexate

*We assumed the serum MTX level before combined IHD and HP was 1500 μmol/L

The reduction rate of MTX is calculated by dividing the difference in serum MTX concentration before and after blood purification by the serum MTX concentration before blood purification. At 2 h after the first combined IHD and HP dialysis, blood collected after the HP cartridge showed an MTX level of 38.92 mol/ml. After the first session of high flux IHD and HP, the plasma MTX concentration had decreased from >1,500 mol/L to 254 mol/L. The MTX reduction rate was 83.8% reduction as we assumed the serum MTX level before first combined IHD and HP was 1500 μmol/L. Continuous Venovenous Hemodiafiltration (CVVHDF) was then started to manage any AKI complications and prevent rebounding of MTX. CVVHDF was performed with Prismaflex machines (Gambro, Lakewood, CO) using Prismaflex M150 (surface area, 1.5 m^2; Gambro). During CVVHDF, a 100% post-dilution mode was adopted with a replacement fluid rate of 3,000 L/h (75 ml/kg/h) and a dialysate flow rate of 2000 ml/h. The serum MTX levels were 117.65, 99.54, 78.58, 62.43 and 48.23 mol/L at 2, 4, 6, 8 and 10 h after the start of the CVVHDF, respectively.

A second session of combined high flux IHD and HP was performed the next day, which reduced the MTX level from 48.23

mol/l to 16.16 mol/L (a 66.5% reduction). Combined high flux IHD and HP was performed once daily for eight days, and CVVHDF was performed continuously following each IHD and HP therapy session. Table 1 shows the efficacy of MTX removal using combined IHD and HP therapy. The patient also developed mucositis and myelotoxicity that was complicated by severe pancytopenia; the white blood cell count declined to 2,900/mm^3, hemoglobin declined to 8.3 g/dl and the platelet count declined to 44,500/mm^3 at 5 days post-HDMTX. Cefepime and teicoplanin were administered for 10 days to treat the sepsis. At day 12 the patient's plasma MTX concentration was 0.74 mol/L. This was concomitant with a marked increase in urinary output and improved signs of myelosuppression. CVVHDF was subsequently ceased at day 12. Leucovorin rescue was discontinued as the MTX level was <0.02 mol/L and renal function recovered slowly to reach baseline at day 20. The serum concentration of MTX and creatinine, as well as the clinical course of purification is shown in Figure 1. On day 25 the patient received resection and reconstruction and she was discharged from hospital without renal dysfunction on day 40.

The patient later continued with chemotherapy with doxorubicin, docetaxel and gemcitabine. Her renal function was BUN 14 mg/dL and creatinine 0.41 mg/dL at 6 months after the AKI insult.

Discussion

Intravenous HDMTX has been recognized as an active agent for treating osteosarcoma. MTX is highly cytotoxic and has multiple potential adverse complications, including mucositis and myelosuppression, as well as renal and liver toxicity. Following its administration, 90% of MTX is excreted unchanged in the urine within 48 h. Two MTX metabolites, 7-Hydroxymethotrexate (7-OH-MTX) and 2,4-Diamino-N10-Methylpteroic Acid (DAMPA) have been identified. Approximately 10% of MTX is converted to 7-OH-MTX by hepatic aldehyde oxidase. 7-OH-MTX is less water soluble than MTX and can also contribute to AKI [13]. Minimal amount of the administered MTX is metabolized to DAMPA by enteric bacteria and is considered clinically inactive.

Elimination of MTX is *via* renal glomerular filtration and active tubular excretion. In the past few years, despite appropriate attention to hydration, urinary alkalinization and leucovorin rescue during the administration of HDMTX, AKI develops in 1.8% to 12% of patients [6]. As >90% of MTX is cleared *via* the kidneys, impairment of renal function contributes to a further delay in the renal excretion of MTX and subsequently leads to sustained systemic toxicity. Therefore, HDMTX induced AKI is a medical emergency.

MTX causes AKI *via* direct effects on the renal tubular by crystallization of MTX and 7-OH-MTX in acidic conditions [14-16], or glomerular injury *via* constriction of the afferent arteriole. Agents that compete for renal tubular secretion, such as TMP-SMX, probenecid, salicylates, penicillins and nonsteroidal anti-inflammatory agents, may inhibit MTX excretion. TMP/SMX is recommended for pneumocystis jiroveci pneumonia prophylaxis during chemotherapy. The interaction between MTX and TMP/SMX is well documented [17,18]. Like MTX, TMP-SMX is an inhibitor of dihydrofolate reductase. TMP-SMX is also known to decrease MTX clearance though its inhibition of tubular secretion. Combined use of MTX and TMP-SMX may result in an increased risk of HDMTX associated side effects. In the current case, the concomitant use of drugs such as TMP-SMX and diclofenac, which could interfere with MTX metabolism, is a possible cause of the unexpectedly high levels of MTX. This was discontinued immediately after AKI occurred.

More recently glucarpidase, a recombinant bacterial enzyme, has been approved for the rapid hydrolysis of MTX into two noncytotoxic metabolites, DAMPA and glutamate. A single dose of glucarpidase has demonstrated efficacy for MTX elimination in patients with delayed excretion of MTX [19,20]. However, the cost and availability limit the use of glucarpidase in patients with HDMTX induced AKI. Glucarpidase is not available in Taiwan. Therefore, extracorporeal removal was initiated immediately after the detection of nephrotoxicity and delayed clearance of MTX; this was continued until the MTX concentration was non-toxic to prevent potentially fatal systemic complications and reverse MTX nephrotoxicity in the present case.

Concurrent pre- and post-treatment hydration and urinary alkalinization are essential for reducing HDMTX toxicity. It is recommended that patients receive at least 2 h of hyperhydration at a minimum of 200 mL/m^2/h or 100 to 150 mL/m^2/h starting 12 h before the start of the HDMTX infusion, and continuing for 24 h to 48 h) or longer after the infusion [16]. Several patient-related factors, such as intravascular volume depletion and chronic kidney disease increase the risk of AKI developing [21]. Vomiting, diarrhea and the use of antiemetics during MTX infusion have been observed in patients with high MTX concentrations and toxicity [22,23]. In the present case, hydration may have been inadequate and could have resulted in a delay in MTX elimination and AKI.

There is no consensus regarding optimal extracorporeal techniques for patients who have markedly high MTX levels and severe AKI. MTX is a relatively small molecule (molecular weight 454 Daltons), which indicates it is a candidate for removal *via* hemodialysis. High flux IHD is likely to be the most effective clearance route for MTX because of its higher blood and dialysate flow rate. However, the protein binding rate of MTX is approximately 50%. It has been reported that MTX has a high intracellular distribution, and therefore notable rebounds of MTX concentrations can occur rapidly after IHD is stopped. In the current case, eight sessions of combined high flux IHD and HP were performed to eliminate both the non-protein-binding and protein-binding MTX. The MTX reduction rate in the 1st, 2nd and 3rd sessions of combined high flux IHD and HP were 83.8%, 66.5% and 52.6%, respectively. Sequential CVVHDF was performed to remove MTX without a rebound in MTX levels. MTX is not a lipophilic compound; consequently, it penetrates lipoidal biomembranes poorly. It has been previously documented that MTX is sequestered in the third spaces, which may prolong its half-life and cause unanticipated toxicity. Extreme caution should be followed when administering MTX to patients with ascites, pleural effusions or pericardial effusion.

To the best of our knowledge, the current study is the first to report a link between AKI and the concomitant use of HDMTX, TMP-SMX, non-steroidal anti-inflammatory drugs and inadequate hydration. Early recognition with cessation of concomitant drugs that could interfere with MTX metabolism is mandatory. In the present case, the patient received eight sessions of combined high flux IHD and HP, and twelve days of CVVHDF in conjunction with leucovorin rescue. She responded quite well to extracorporeal removal with a substantial reduction in MTX levels. The effectiveness of IHD and HP as well as CVVHDF in reducing MTX levels is well established.

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