

MISCELLANEA

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CONTINUOUS VENO-VENOUS HEMODIAFILTRATION IN METHOTREXATE INTOXICATION

CIĄGŁA ŻYLNO-ŻYLNA HEMODIAFILTRACJA W ZATRUCIU METOTREKSATEM

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Abstract

Methotrexate is a highly nephro- and hepatotoxic drug used in osteosarcoma treatment protocols, in children and adults. High dose methotrexate therapy may lead to kidney injury and decrease of methotrexate clearance, followed by an increase of its serum concentration. As a result, systemic intoxication may develop. Prophylaxis based on intensive fluid therapy and urine alkalization may not be sufficient to prevent the formation of methotrexate crystals in kidney tubules.

The aim *of the study was to present three cases of methotrexate intoxication treated with continuous veno-venous hemodiafiltration.*

Patients and methods**:** *Three children aged 9-16 years old with tibial or fibular osteosarcoma were admitted to the Nephrology Department due to severe methotrexate intoxication. All children presented with multiorgan injury, including liver, kidney, gastrointestinal tract and bone marrow impairment. Methotrexate concentration, 24 hours after drug administration, was 660-1238 μmol/L. Although intensive fluid therapy, urine alkalisation and administration of high doses of folinic acid (leucovorin), methotrexate serum concentration remained toxic. Effective reduction of methotrexate concentration (<1.5 μmol/L) was achieved 24-156 hours after CVVHDF initiation. Kidney and liver function recovered completely in all of the patients.*

Conclusion: *Continuous veno-venous hemodiafiltration is an effective supportive method in methotrexate elimination in patients with severe intoxication.*

Key words: *methotrexate, children, osteosarcoma, continuous veno-venuous hemodiafiltration*

Streszczenie

Metotreksat jest lekiem nefro- i hepatotoksycznym stosowanym w leczeniu mięsaka kościopochodnego u dzieci i dorosłych. Terapia dużymi dawkami metotreksatu może prowadzić do niewydolności nerek i obniżenia klirensu leku, a w następstwie tego do wzrostu stężenia metotreksatu we krwi i zatrucia. Stosowanie profilaktycznego intensywnego nawadniania chorych i alkalizacja moczu może okazać się postępowaniem niewystarczającym dla zapobieżenia formowaniu się kryształów metotreksatu w cewkach nerkowych.

Celem pracy *było przedstawienie trzech przypadków zatrucia metotreaksatem leczonych za pomocą ciągłej żylno-żylnej hemodiafiltracji.*

Pacjenci i metody: *Troje dzieci w wieku 9-16 lat z mięsakiem kościopochodnym zlokalizowanym w kości piszczelowej lub strzałkowej było przyjęte na oddział nefrologii z powodu ciężkiego zatrucia metotreksatem z objawami uszkodzenia wątroby, nerek, przewodu pokarmowego i szpiku. Stężenia metotreksatu 24 godziny po podaniu wynosiły 660-1238 μmol/L. Mimo stosowania intensywnego nawadniania, alkalizacji moczu i podawania dużych dawek folinianu wapnia stężenia metotreksatu*

pozostawały wysokie i utrzymywały się objawy zatrucia. Poza stosowaniem ww. leczenia rozpoczęto ciągłe oczyszczanie pozaustrojowe metodą ciągłej żylno-żylnej hemodiafiltracji uzyskując obniżenie stężenia metotreksatu <1,5 µmol/L po 24-156 godz. prowadzenia zabiegu.

Wniosek: *Ciągła żylno-żylna hemodiafiltracja jest skuteczną metodą wspomagającą eliminację metotreksatu u chorych z ciężkim zatruciem.*

Słowa kluczowe: metotreksat, dzieci, mięsak kościopochodny, ciągła żylno-żylna hemodiafiltracja

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INTRODUCTION

The outcome of patients with osteosarcoma has improved greatly since 1972, when methotrexate (MTX) was introduced to malignancies-treatment protocols. Unfortunately high dose methotrexate therapy (HDMTX) is burdened by high toxicity to liver and kidneys. Because MTX elimination may be affected by administration of other medications, its toxicity vary among different anticancer treatment protocols. Pediatric patients, especially younger than 15 yrs., are known to tolerate MTX better than adults. As a result the standard dose varies from 8 g/m^2 in adults to 12 g/m^2 in children. However, in some patients who metabolize MTX slow, its plasma concentration may arise above the recommended limits.

In order to prevent toxic side effects, MTX plasma concentration should be constantly monitored, patient should be intensively hydrated and urine should be alkalized (MTX crystallizes in renal tubules in acid urine) by sodium bicarbonate. Twenty four hours after MTX infusion, calcium folinate (leucovorin) should be administered. It does not decrease MTX plasma concentration but reduces especially myelotoxicity [1]. Although the protocols to reduce HDMTX toxicity are well established and widely used, acute kidney injury (AKI) occurs in 1.8% of all patients. Because more than 90% of administered MTX dose is normally excreted by kidneys, AKI potentates toxicity of the drug and its metabolites [2]. According to the adjuvant chemotherapy programme – EURAMOS, the levels of MTX >20 µmol/L – 24 hours after administration, >2 µmol/L after 48 hours and >0.2 µmol/L after 72 h are associated with higher toxicity.

More rapid decrease of MTX concentration (>98%) might be obtained by carboxypeptidase G2 (glucarpidase), a recombinant enzyme that dissolves MTX and 7-OH-MTX to nontoxic metabolites within several minutes after its administration. Although it has been already used in single cases of MTX intoxication and seemed to be safe and well tolerated, it is not yet available in everyday practice. The drug is undergoing final stages of clinical trials [3, 4].

The efficacy of extracorporeal therapy in MTX removal is uncertain. While hemodialysis is known to be less effective, continuous renal replacement therapy (CRRT) especially hemodiafiltration (HDF) may be helpful in extremely serious cases.

The aim of the study was to present 3 cases of MTX intoxication in children with osteosarcoma, in whom hemodiafiltration was used as a method of extracorporeal drug removal.

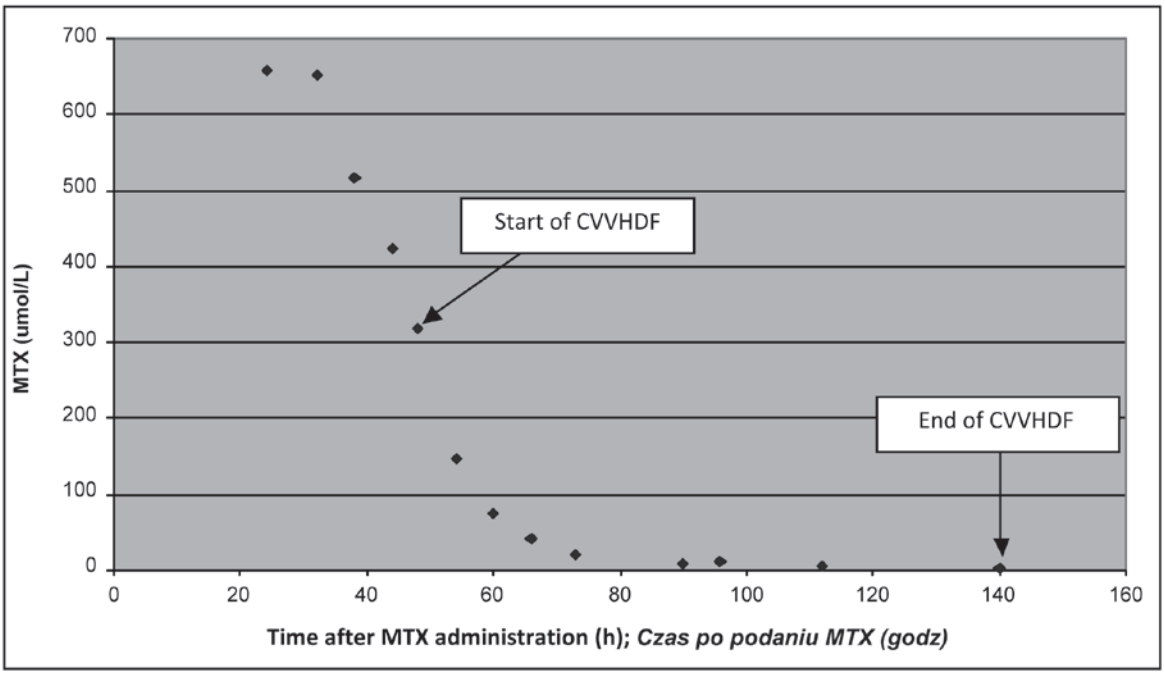
METHODS

Blood, urine and dialysate (obtained from effluent bag during HDF) specimens were analyzed. Continuous veno-venous hemodiafiltration (CVVHDF) was performed on PRISMA machine (Gambro) with PRISMA SET M100 hemofilters. The mean blood flow was 100 ml/min and the mean dialysate flow was 1000 ml/hour. Anticoagulation was obtained by heparin, to maintain ACT between 180-220 sec. HEMOSOL (Gambro) was used as dialysate and replacement fluids.

MTX serum concentration was measured with immunoenzymatic test – Emit Methotrexate Assay by Siemens, on Vitros 5600 analyzer (Ortgo clinical Diagnostics, Johnson and Johnson Company). Biochemical analysis (urea, creatinine, aminotransferases, gamma-glutamyl transpeptidase, bilirubin, total protein, albumin) were done by the dry chemistry method on Vitros 500 analyzer (Ortho clinical Diagnostics, Johnson and Johnson Company). Arterial blood gases were measured on Premier GEM 4000 analyzer (Instrumentation Laboratory). Coagulation parameters were measured in citrated plasma on CS-2100i analyzer (Sysmex) or BCS XP (Siemens). Complete blood count was measured in EDTA-plasma on LH 750 analyzer (Beckman Coulter). Urinalysis was performed by Clinitek Advantus (Siemens).

CASE 1

Nine y.o. boy (45 kg, BSA 1.4 m^2) presented with the past history of left fibula osteosarcoma (osteosarcoma osteoblasticum partim microcellulare G3) 2 years after macroscopically radical surgery of the tumor with fibular nerve. Because of local recurrence and pulmonary metastases he was treated with amputation of lower extremity and chemotherapy (CARBO + VP 16). Due to progression, the therapy was changed and intravenous MTX was administered in the dose of 11.42 g/m^2. At the beginning of the treatment, glomerular filtration rate (GFR) was 135 ml/min/1.73 m^2. Four hours after MTX administration serum level was 2910 µmol/L, and after next 24 hours – 660 µmol/L. He was then transferred to Nephrology Department of University Children's Hospital. During first 24 hours conservative management was conducted (intensified fluid therapy, urine alkalization and 800 mg/24 h of leucovorin infusion). Because of deterioration of kidney function and persistent high levels of MTX, 48 hours after drug administration hemodiafiltration was started. The extracorporeal



MTX level *Poziom MTX* (µmol/L)	Time after MTX administration (h) *Czas po podaniu MTX (godz)*													
	4	**24**	**32**	**38**	**44**	**48**	**54**	**60**	**66**	**73**	**90**	**96**	**112**	**140**
serum, *surowica*	2910	660	654	516	424	318	147	75	40	20.2	8.6	9.8	3.6	1.5
dialysate *dializat*	-	-	-	-	-	-	-	-	13.7	-	-	-	2.04	-

Fig. 1. Serum and dialysate MTX levels in patient number 1.

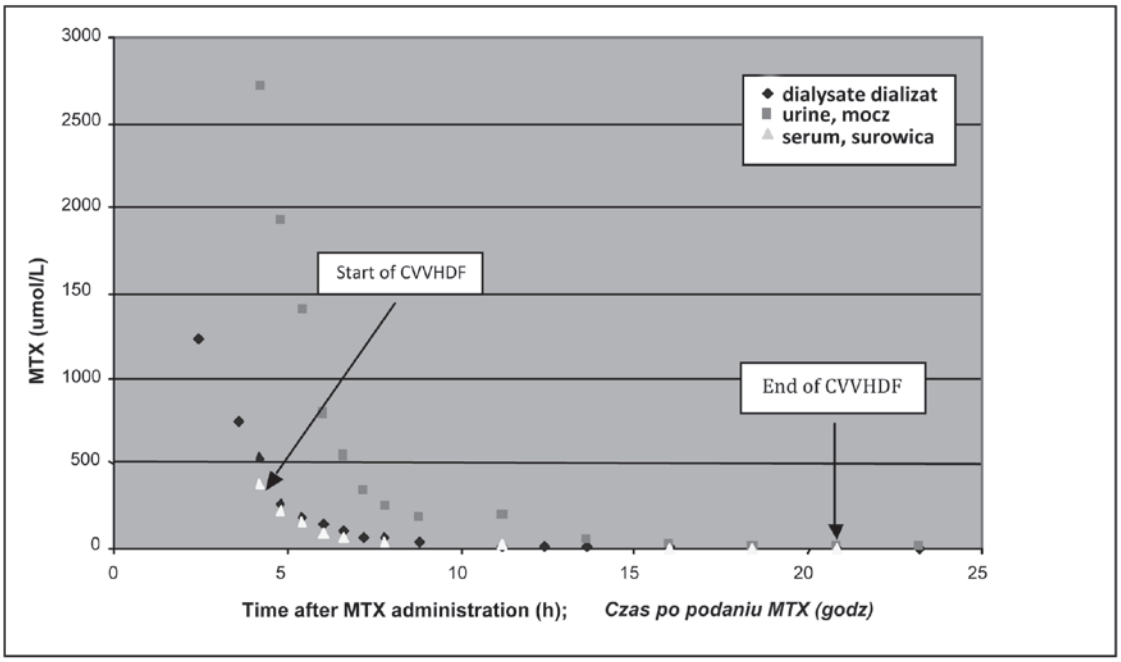
Ryc. 1. Stężenia metotreksatu (Mtx) w surowicy i dializacie u pacjenta nr 1.

therapy was being performed continuously during next 92 hours. At the same time intensified fluid therapy, leucovorin, liver sparing agents and parental alimentation were continued. Both kidney and liver function parameters normalized gradually during therapy and patient was transferred back to Oncology Department of Mother and Child Institute. Chemotherapy (vincristin, DTIC, ADM, CTX) was started once more, followed by 2 BCD courses. Unfortunately, in spite of aggressive therapy, continuous progression of the osteosarcoma did not stop and the boy died after 5 months.

CASE 2

Sixteen y.o. girl (weight 48 kg, BSA 1.5 m^2) presented with osteosarcoma localized in left tibia (osteosarcoma G3, MFH-like type, osteoblastic) was enrolled in EURAMOS program. At the beginning of treatment, GFR was 188 ml/min/1,73 m^2. In 9-th week of treatment she was administered MTX in the dose of 12 g/m^2 (18.3 g). Shortly after, she presented with persistent vomiting, edema and lack of diuretic response to furosemide. Because of high MTX serum level (>1000 µmol/L within first 24 hours), she was transferred to Nephrology Department of University Children's Hospital. At the beginning she was treated conservatively. Since the following day, due to deteriorating kidney (GFR 23 ml/min/1.73 m^2) and liver function accompanied by sustained high MTX serum levels, hemodiafiltration was performed. As in the first case, intensive fluid therapy was continued (achieving diuresis of 10 L/day) together with high doses of leucovorin (2000 mg/day), urine alkalization and parenteral alimentation (lasting 6 days). HDF was for the next 156 hours which resulted in significant decrease of serum MTX level. During HDF treatment patient required 4U of packed red blood cells, 1U of packed platelets and 1U of fresh frozen plasma. Kidney as well as liver function improved greatly (GFR 68 ml/min/1,73m^2, GOT 45 U/L, GPT 155 U/L) within 6 days. One month after acute kidney injury and acute liver failure incident, the tumor was surgically removed and a modular, oncological endoprotese was implemented.

The chemotherapy was changed to EORTC program; 3 full dose postoperative courses were administered. Treatment was accomplished within 6 months. The following year kidney and liver function parameters remained within normal ranges. There is no sign of tumor metastases on imagining examination.



MTX level *Poziom MTX* (µmol/L)	Time after MTX administration (h) *Czas po podaniu MTX (godz)*														
	24	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**88**	**112**	**124**	**136**	**184**	**208**
serums ***urowica***	1238	739	530	268	182	139	93	61	59	39	12	11	7	2	1.1
dialysate ***dializat***	-	-	379.6	219	150	93	59	-	34	-	14	-	-	1.5	0.87
urine ***mocz***	-	-	2716	1929	1399	792	550	345	243	189	194	-	55	12	9.37

Fig. 2. Serum, dialysate and urine MTX levels in patient number 2.

Ryc. 2. Stężenia metotreksatu (MTX) w dializacie, moczu i surowicy u pacjentki nr 2.

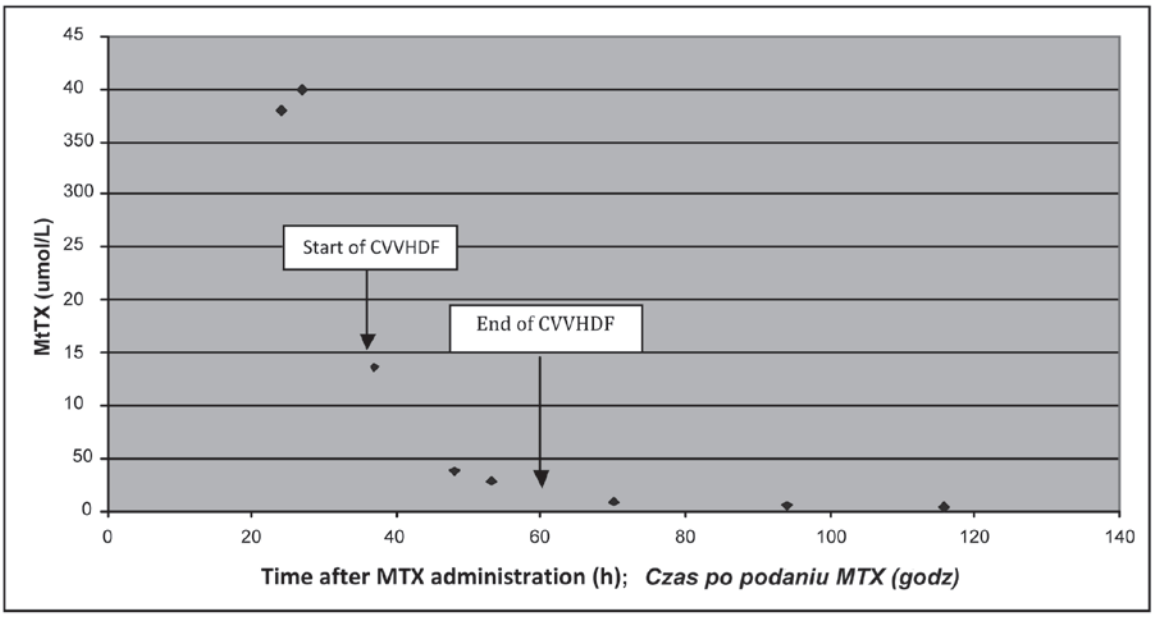
CASE 3

Fifteen y.o. girl (weight 55 kg, height 161 cm, BSA 1.6 m^2) presented with osteosarcoma of left femur (low grade intramedullary osteosarcoma), suspected of having metastases in right lung was administered 12 g/m^2 (18,8 g) of MTX according to EURAMOS program in 4-th week of treatment. Before MTX administration GFR was 145 ml/min/1.73 m^2. She was admitted to the Nephrology Department of University Children's Hospital because of MTX intoxication. During day one she was unsuccessfully treated conservatively (intensified fluid therapy, leucovorin and urine alkalization). Due to increasing MTX serum levels and deterioration of kidney (GFR 37 ml/min/1.73m^2) and liver function, 37 hours after MTX administration, HDF was initiated. The extracorporeal decontamination was being continued through the next 24 hours, after which serum MTX level and biochemical parameters decreased significantly. Fluid therapy, urine alkalization and leucovorin infusions in the dose adjusted to MTX serum level were continued also after HDF. The patient needed 1 packed red blood cells transfusion. Three weeks after intoxication, chemotherapy was ordered once more, but the treatment course consisted only of AP (Adriamycin 75 mg, Cisplatin 120 mg/m^2). After 2 months more a radical surgery was performed with endoprotesoplasty. Histopathology examination of the tumor confirmed previous diagnosis, that it is a low grade osteosarcoma G1/G2, necrotized in 83,8%. The patient is now continuing chemotherapy in a modified regime without MTX. Her kidney and liver function parameters remain within normal ranges.

In all three patients bone marrow disorders with leucopenia, anemia (Tables I-III) and serious damage of gastrointestinal tract epithelium with oral mucous membrane ulcers and bleeding from upper and lower digestive tract were observed. Urine alkalization to pH > 7 was obtained by administration of 8.4% $NaHCO_3$ intravenously in the dose of 2 ml/kg/24 hours.

DISCUSSION

MTX is an analogue and antimetabolite of folic acid, which is essential to purin and pirymidin synthesis. It is



MTX level *Poziom MTX* (µmol/L)	Time after MTX administration (h) *Czas po podaniu MTX (godz)*							
	24	**27**	**37**	**48**	**53**	**70**	**94**	**116**
serum *surowica*	380	400	137	38.8	29	9.2	5.2	4.25

Fig. 3. Serum MTX levels in patient number 3.

Ryc. 3. Stężenia metotreksatu (MTX) w surowicy u pacjenta nr 3.

Table I. Laboratory tests results of patient number 1 in succeeding days after MTX administration.

Tabela I. Wyniki badań laboratoryjnych u pacjenta nr 1 w kolejnych dobach od podania metotreksatu.

Laboratory tests *Wyniki badań laboratoryjnych*/Results	Days after MTX administration *Dni po podaniu MTX*				
	2	3	4	5	6
Urea; *mocznik* (mg/dL)	72.3	78.8	24	15	11.9
Creatinine; *kreatynina* (mg/dl)	2.3	2.7	1.3	0.9	0.6
AST (U/L)	2696	---	---	678	289
ALT (U/L)	1733	---	---	1570	905
GGTP (U/L)	---	---	---	333	268
Bilirubin; *bilirubina* (mg/dL)	---	---	---	3.9	3.1
INR	---	2.07	---	---	---
d-dimer (ug/L FEU)	---	398	---	---	---
Fibrinogen; *fibrynogen* (g/L)	---	3.84	---	---	---
Ca (mmol/L)	---	3.4	---	4.4	4
PLT (x10^3/uL)	219	181	180	109	62
WBC (x10^3/uL)	8.4	6.9	4.4	4	1.2
Hgb (g/dL)	10.9	10.3	11.7	8.5	7.7

AST – aspartate transaminase, *aminotransferaza asparaginianowa*; ALT – alanine transaminase, *aminotransferaza alaninowa*; GGTP – gamma-glutamyl transpeptidase, *gamma-glutamylotranspeptydaza*; INR – international normalized ratio, *wskaźnik czasu protrombinowego*; Ca – calcium, *wapń*; PLT – platelet count, *płytki krwi*; WBC – white blood count, *krwinki białe*; Hgb – hemoglobin, *hemoglobina*

Table II. Laboratory tests results of patient number 2 in succeeding days after MTX administration.

Tabela II. Wyniki badań laboratoryjnych u pacjenta nr 2 w kolejnych dobach od podania metotreksatu.

Laboratory tests ***Wyniki badań laboratoryjnych/ Results***	**Days after MTX administration/*Dni po podaniu MTX***									
	2	3	4	5	6	7	8	9	10	11
Urea; *mocznik* (mg/dL)	61	53	28	29	34	32	28	21	41	42
Creatinine; *kreatynina* (mg/dL)	3	2.5	1.7	1.7	1.8	1.3	1	0.8	1.1	1
Uric acid; kwas moczowy (mg/ dL)	7	4,5	---	---	---	---	---	---	---	---
AST (U/L)	1768	1199	460	136	76	55	59	53	49	45
ALT (U/L)	2114	2112	1211	782	593	439	336	235	189	155
Bilirubin; *bilirubina* (mg/dL)	2.9	3.9	4.2	3.1	2.5	2	---	1.2	---	---
INR	1.33	3.03	1.39	1.36	1.13	1.06	---	1.02	1	0.98
d-dimer (ug/L FEU)	9933	9658	708	---	807	1300	---	2088	2163	3898
fibrinogen (g/L)	1.74	1.94	3.61	---	4.22	4.33	---	3.86	3.37	3.93
Ca (mmol/L)	3.7	3.9	4.4	5.9	5.8	5.5	5.3	5.1	4.3	4.1
PLT (x10^3/uL)	96	105	63	52	45	28	20	8	9	34
WBC (x10^3/uL)	6.1	5.3	3	1.7	1.5	1.6	1.8	1.3	2.3	3.2
Hgb (g/dL)	8.1	8.3	7.6	8.4	10.1	10.2	9.3	8.3	8.5	9.1

AST – aspartate transaminase, *aminotransferaza asparaginianowa*; ALT – alanine transaminase, *aminotransferaza alaninowa*; GGTP – gamma-glutamyl transpeptidase, *gamma-glutamylotranspeptydaza*; INR – international normalized ratio, *wskaźnik czasu protrombinowego*; Ca – calcium, *wapń*; PLT – platelet count, *płytki krwi*; WBC – white blood count, *krwinki białe*; Hgb – hemoglobin, *hemoglobina*

Table III. Laboratory tests results of patient number 3 in succeeding days after MTX administration.

Tabela III. Wyniki badań laboratoryjnych u pacjenta nr 3 w kolejnych dobach od podania metotreksatu.

Laboratory tests ***Wyniki badań laboratoryjnych*/Results**	**Days after MTX administration/*Dni po podaniu MTX***				
	2	**3**	**4**	**5**	**6**
Urea, *mocznik* (mg/dL)	32	26	17	26	32
Creatinine, *kreatynina* (mg/dL)	1,8	1.4	1.3	1.5	1.4
Uric acid, *kwas moczowy* (mg/dL)	8,4	---	---	---	---
AST (U/L)	4688	1897	373	278	147
ALT (U/L)	5560	3923	1927	1376	981
GGTP (U/L)	143	133	102	---	---
Bilirubin, *bilirubina* (mg/dL)	2.6	2.9	1.3	1.2	---
INR	1.58	1.8	1.2	1.11	---
d-dimer (ug/L FEU)	6904	5160	1908	3210	---
fibrinogen (g/L)	2.45	2.67	3.05	3.39	---
Ca (mmol/L)	4.1	4.7	4.4	4.3	---
PLT (x103/uL)	284	218	192	154	121
WBC (x103/uL)	5.7	5.2	3.8	2.8	1.5
Hgb (g/dL)	11.1	11.6	9.8	9.6	9.6

AST – aspartate transaminase, *aminotransferaza asparaginianowa*; ALT – alanine transaminase, *aminotransferaza alaninowa*; GGTP – gamma-glutamyl transpeptidase, *gamma-glutamylotranspeptydaza*; INR – international normalized ratio, *wskaźnik czasu protrombinowego*; Ca – calcium, *wapń*; PLT – platelet count, *płytki krwi*; WBC – white blood count, *krwinki białe*; Hgb – hemoglobin, *hemoglobina*

one of the oldest and most commonly used cytostatic. High doses are used in chemotherapy in children and adults and smaller doses, as an immunosuppressive agent, in rheumatology. As a component of multidrug therapy protocols it is used in oncology in treatment of acute lymphoblastic leukemia, non-Hodgkin lymphoma and osteosarcoma. MTX is highly toxic, especially to liver, kidney and bone marrow. According to current guidelines, in order to prevent from its side effects, leucovorin should be administered in the dose adjusted to serum MTX levels.

In spite of systematical measurements, there are patients who achieve MTX levels, which are much higher than recommended [3, 4, 5]. Such situation occurred in three children with osteosarcoma introduced above. Although each child presented different signs and symptoms of intoxication, all of them developed acute kidney and liver failure. MTX is excreted unchanged with urine in 50-80% within first 12 hours after administration and up to 95% within 48 hours [6]. Presence of kidney injury highly contribute to an increase in MTX serum level, even when it is administered in small doses.

The main mechanism of kidney injury is precipitation of MTX in renal tubules, which is increased if the urine is acid. That is why, one of the main nephroprotective mechanisms against MTX toxicity is urine alkalization. Apart from crystals creation within the lumen of renal tubules nephrotoxicity of MTX is caused by its direct effect on tubules and glomeruli and disorders of resistance of the afferent arteriole that leads to decrease in kidney perfusion [3]. Nowadays, while following protocols against MTX toxicity (urine alkalization, leucovorin administration), the incidence of acute kidney injury is about 1.8%, with mortality rate of 4.4% (0.08% of all patients treated with high doses of MTX).

Except for acute kidney injury, individual predispositions due to genetic polymorphism of MTX metabolism, may increase MTX toxicities and potentate its side effects. The best known is the polymorphism of metylenotetrahydrofolian reductase [7]. It is proven that some of the dihydrofolian and gamma-glutamylohydrolase polymorphisms are associated with grater MTX myelotoxicity [8].

In all reported cases the levels of MTX highly exceeded the recommended values. The highest levels, 24 hours after MTX administration, were observed in patient No 2. During CVVHDF in this child levels of MTX in blood, dialysate and urine were precisely monitored. Because of persistence of biochemical abnormalities, oncological treatment had to be held for 5 weeks, after which the girl undergone radical surgery. Histopathology examination of the tumor shown necrosis and regression of cancer tissue in 99.5%. MTX levels observed in other two patients were also reported by other authors [2, 9]

The decision to indicate extracorporeal methods, as a supportive way of MTX excretion, in reported cases was made because high MTX levels coexisted with acute kidney injury. So far different types of dialysis-based methods have been attempted in treatment of MTX intoxication. Although peritoneal dialysis has low effectiveness in MTX removal [10], multiple fluid exchanges may improve drug elimination, especially in critically ill patients, when other extracorporeal removal techniques are contraindicated [11].

The most efficient method of extracorporeal removal is hemodialysis (HD) with indication of high permeability membranes (high-flux hemodialysis). This method allows to excrete 75.7% (42-94%) of MTX [12, 13] within 3-5 hours. Unfortunately shortly after finishing the procedure, serum MTX levels rebound to 10-221% [13]. HD may be also difficult to perform in critically ill, unstable patients in whom continuous methods would be a better choice.

Administration of continuous hemodiafiltration in reported cases allowed to eliminate the drug effectively, what was confirmed by the levels of MTX in dialysate of our second patient. Additionally, it helped to improve general condition and permitted to use uninhibited fluid therapy including parenteral alimentation. Because in all our patients urine output was preserved, it remained the main way of MTX excretion (fig. 2). MTX level was measured in dialysate to help us make therapeutic decision about continuing or abounding CVVHDF. Based on our reported data and other authors outcomes [14], HDF as a combination of two methods of molecules removal (convection and diffusion) may be a useful treatment technique in severe MTX intoxication. Performing CVVHDF may play a crucial role in MTX elimination in anuric patients.

CONCLUSION

Continuous veno-venous hemodiafiltration is an effective supportive method in methotrexate elimination in patients with severe intoxication.

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