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Original article

The Influence of Detoxification Agents on the Intensity of Side Effects Caused by Medium-high Doses of Methotrexate in Children with Acute Lymphoblastic Leukemia: Case Series

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SUMMARY

Objective The treatment of childhood acute lymphoblastic leukemia (ALL) in Serbia is conducted according to protocol ALL IC BMF-2009. The therapy includes the application of cytostatic drugs methotrexate and 6-mercaptopurine, and drug detoxifying Calcium Folinate. At the moment, 80% of affected children could be cured with current treatment, but resistance to the therapy and its toxic effects remain serious clinical problems. The aim of the study was to investigate the influence of detoxification agents (Calcium Folinate, silymarin and ursodeoxycholic acid) on the side effects of methotrexate, applied in this protocol.

Methods A modified acute toxicity form (GPOH) was used for side effects monitoring. The research included children with either standard or intermediate risk ALL in the consolidation therapy phase, who were hospitalised at the Institute for Child and Youth Health Care of Vojvodina in Novi Sad during the period from July 2010 to February 2011.

Results The most frequent side effect after 40 applications of methotrexate in ten children was bone marrow depression. Methotrexate caused: leukopenia in 10 patients, thrombocytopenia in 5 patients; after the use of folic acid, platelet count grew in 8 patients, leukocyte in 2 patients. Less frequent side effects: an increase serum transaminase activity, the state of fever, bronchopneumonia, diarrhoea with mild cramps and hypercalcaemia.

Conclusion The application of Calcium Folinate, silymarin and ursodeoxycholic acid prevented the occurrence of severe adverse effects caused by medium-high doses of methotrexate. Observed adverse effects were of mild to moderate intensity, reversible and did not significantly disturb the quality of life in treated patients.

Keywords: acute lymphoblastic leukemia; methotrexate; Calcium Folinate; silymarin; ursodeoxycholic acid

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a malignant disease which represents 25% of all malignancies in children [1]. About 80% of all affected can be cured, but resistance to the therapy and its toxic effects remain serious clinical problems [2]. The most used form of treatment is chemotherapy that includes methotrexate (MTX). MTX is an antagonist of folic acid and is essential in the treatment of ALL [3]. The problem with MTX, as with the other chemotherapeutics, is the selectivity of its mechanism. MTX is applied in the consolidation phase of the therapy. As a consequence, there is inhibition of both growth and proliferation of non-cancerous cells. MTX destroys the cells in the mitosis, which is particularly important for an organism in development and can be the cause of permanent complications [4]. Those effects occur in the S-phase of the cell cycle; hence the most significant cytotoxic effects happen when the cell is rapidly dividing itself. Since these are the cells of the bone marrow, the chemotherapy results in leukopenia, anaemia and thrombocytopenia. It also affects the lining of the digestive tract, which is followed by mucositis, stomatitis, gastrointestinal bleeding [5].

The induction of Calcium Folinate (leukovorin) in the therapy of ALL significantly improved the tolerance of this drug, as well as the results of treatment. Calcium Folinate is a 5-formyl derivative of tetrahydrofolic acid that does not require the activity of dihydrofolate reductase. Therefore, Calcium Folinate retains its activity during the application of antagonists of folic acid and manages processes of DNA synthesis that are inhibited by MTX [6]. However, an increased dose of Calcium Folinate may reduce the response to the therapy since it inhibits the effect of MTX. How to determine the best combined dosage of MTX and Calcium Folinate in order to prevent complications of treatment while retaining the effect of drugs on the leukemic cells is still a topical issue and a key subject of discussion about implementation of innovations in protocols [7].

The aim of the study was to monitor the tolerability of MTX and the importance of application of antidote, Calcium Folinate, and silymarin and ursodeoxycholic acid as detoxification agents, in order to reduce intensity of the adverse effects that occur during the consolidation phase to the ALL IC-BMF 2009 protocol, in children with ALL.

METHODS

Adverse effects of MTX in children with ALL hospitalized at the Institute for Child and Youth Health Care of Vojvodina in Novi Sad, were monitored from July 2010 to February 2011. Research included children who were diagnosed with standard or intermediate risk ALL (SR/IR) (Table 1).

The treatment of children was conducted according to ALL-BMF IC 2009 protocol, which includes the use of cytotoxic drugs – MTX and 6-mercaptopurine, and detoxification agent – Calcium Folinate in the consolidation phase (Table 2). Number of application of MTX was 40.

The treatment also includes the routine use of antiemetics, granisetron (Kytril ampoules), applied immediately before and 12 hours after MTX application, and additionally 1-2 times a day, if needed in the following days, in cases of nausea. $NaHCO_3$ infusion is routinely applied with the use of MTX in order to ensure proper hydration and prevent the decline in blood pH. With the approval of the Ethics Committee, we

Table 1. Characteristics of patients with ALL

Group of standard risk	Age range of 1 to 6 years
	White blood cell count is less than 20000/μL
	The status of the bone marrow is M1 or M2 – 15th day of therapy and M1 – 33rd day of therapy
	The number of peripheral blood blasts is less than 1000/μL
	At the time of diagnosis there is no CNS infiltration
Group of intermediate risk	Patients younger than 1, and older than 6 years
	White blood cell count greater than 20000/μL
	The status of the bone marrow is M1 or M2 – 15th day of therapy and M1 – 33rd day of therapy or M3 – 15th day of therapy and M1 – 33rd day of therapy
	The number of peripheral blood blasts is less than 1000/μL

M1 – bone marrow blasts: <5%; M2 – bone marrow blasts: 5–25%; M3 – bone marrow blasts: ≥25%

Table 2. Consolidation phase in ALL BMF IC-2002 protocol

Drugs	Dose	Method of application
MTX	2 g/m^2	I.v. in four divided doses, every 14 days
	6-12 mg (age dependent)	Intrathecally, 30 minutes after the start of MTX infusion
6-MP	25 mg/m^2/day	Per os, 56 days
Ca-folinate	15 mg/m^2	I.v. 42 h, 48 h i 54 h after application of MTX

MTX – methotrexate; 6-MP – 6-mercaptopurine; Ca-folinate – Calcium Folinate

Table 3. Adverse effects, their frequency and intensity in consolidation phase

Adverse effects	Number of patients	State of patients	Intensity (1-4)
Hematologic toxicity	10	Leukopenia, thrombocytopenia	2
Febrile state	3	38–39°C	1
Hepatotoxicity	2	Elevated enzyme value ALT, AST, GGT	1
Infection	1	Bronchopneumonia	2
Gastrointestinal toxicity	1	Diarrhea five times a day	2
Metabolic disorder	1	Hypercalcemia – 2,7 mmol/L	1

ALT – alanine aminotransaminase, AST – aspartate aminotransaminase; GGT – gamma glutamyl transaminase

gained access to the medical records of children with ALL, which included the state of examined patients in the consolidation phase. The state of the patients was observed throughout the period between the two applications of MTX. The observation lasted for two weeks, so we were able to monitor the condition of the patients immediately after the application of MTX and the antidote Calcium Folinate. Adverse effects were observed using a modified form for monitoring the acute toxicity of the therapy, which was recommended by NCI CTC (National Cancer Institute Common Toxicity Criteria) and modified by GPOH (Society for Paediatric Oncology and Haematology).

The form included the following side effects, which may occur during treatment: infection (temperature), gastrointestinal toxicity (nausea, vomiting, stomatitis, diarrhoea), hepatotoxicity (S-bilirubin, S-ALT/S-AST), nephrotoxicity (creatinine, proteinuria, haematuria, creatinine clearance), cardiotoxicity (arrhythmias, cardiac function, echocardiography: LVSF), neurotoxicity (central neurotoxicity, peripheral neurotoxicity), skeletal toxicity: acute and chronic (osteonecrosis), other adverse effects (such as hematologic toxicity, metabolic disorder).

Every adverse reaction was divided into four levels according to the severity of symptoms.

Data were collected and analysed by examining the medical records with doctors who applied the therapy, which required going to the Department of Haematology once a week. The collected data were analyzed and presented quantitatively and qualitatively.

RESULTS

During the study period, from July 2010 to February 2011, ten patients (6 girls and 4 boys) with standard or intermediate risk ALL received consolidation therapy at the Department of Haematology. We have obtained data on adverse effects that occurred during the consolidation phase, their frequency and intensity, using the form for monitoring the acute toxicity of the therapy. Haematological toxicity was observed in all 10 patients (100% of cases) with decreased number of platelets and leukocytes (Table 3). Changes in the number of platelets and leukocytes during the four applications of MTX are shown in Tables 4 and 5.

The Table 4 shows the average value and standard deviation of the number of leukocytes for all 4 MTX applications immediately after the application of MTX and after the application of Calcium Folinate, in all 10 patients. The results show that the number of leukocytes was below the reference value (4.5-15×10^9/L) in all 10 patients. An increased number of leukocytes was noticed 24 hours after the application of Calcium Folinate in the case of two patients (patients No 9 and 10), while leukocyte count of other patients was decreased in regard to pretreatment values. Leukocyte count reached normal values in the period between the two applications of MTX, which lasts 14 days.

The Table 5 shows the average value and standard deviation of the number of platelets in all 10 patients for all 4 applications of MTX, immediately after the application of the drug and

Table 4. Changes in the number of leukocytes after application of MTX and Calcium Folinate (mean value ± standard deviation)

Patient No.	Immediately after application of MTX	Immediately after application of Ca-folinate
1	3.85±1.18	3.48±0.38
2	4.67±4.04	3.53±3.06
3	4.50±1.99	2.93±1.89
4	5.77±0.69	4.00±0.88
5	3.52±0.88	2.23±0.74
6	3.32±0.92	2.40±0.98
7	5.55±0.55	3.30±0.80
8	3.45±0.85	3.38±2.16
9	2.77±1.02	3.08±2.14
10	3.15±1.14	3.63±1.58

Table 5. Changes in the number of platelets after application of MTX and Calcium Folinate (mean value ± standard deviation)

Patient No.	Immediately after application of MTX	Immediately after application of Ca-folinate
1	243.25±21.45	244.75±52.89
2	121.75±63.73	183.00±55.34
3	149.50±57.47	126.25±47.95
4	210.00±47.80	257.00±21.62
5	139.25±87.01	144.50±49.68
6	187.75±77.36	199.00±34.16
7	122.50±31.78	168.75±12.99
8	237.50±68.69	253.75±59.72
9	105.75±60.17	140.75±64.19
10	230.25±54.56	215.75±71.79

Calcium Folinate. Use of MTX caused a decrease in the platelet count below reference values (150-450×10^9/L) in five patients. However, after the application of Calcium Folinate, in eight out of the ten patients, the number of platelets increased. In two patients (patients No 3 and 10) the number of platelets was decreased in the period of 24 hours after application of the antidote. The decrease in the number of platelets did not required platelet transfusion.

Fever (38-39°C) occurred in three patients after the first, the second and the fourth application of MTX. An infectious complication, bronchopneumonia, developed in one patient after the fourth dose of MTX. The causative agent was not isolated. After antibiotic treatment (ceftriaxone, amikacin and clarithromycin) and administration of antifungal drug (fluconazole) complete recovery was achieved.

Gastrointestinal toxicity with diarrhoea occurring up to five times a day with mild abdominal cramps was observed in one patient after the first dose of MTX. The situation was balanced over a short period without additional therapy.

Elevated liver enzymes alanine aminotransaminase (ALT), aspartate aminotransaminase (AST) and gamma glutamyl transaminase (GGT) indicated the existence of hepatotoxicity. Elevated values were up to three times higher than the upper reference value. Liver function impairment has withdrawn after the application of silymarin and ursodeoxycholic acid. Disorder of these parameters was observed after the first and the second dose of MTX.

Metabolic toxicity was observed in one patient after the application of the second dose of MTX in the form of elevated level of calcium, which amounted to 2.7 mmol/L. This disorder did not require additional therapy and after a short period calcium level returned to normal.

DISCUSSION

The prospective study was carried out at the Department of Haematology from July 2010 to February 2011, and was comprised of ten children who had a disease of the standard or intermediate risk. A small number of patients involved in the research are consistent with the data on the incidence of this disease in children. It is expected that nearly four to five new ALL cases per 100,000 children will occur each year, mostly between the ages of 2 to 5 years [8].

Before Calcium Folinate was introduced into leukemic treatment protocol, applied therapy was followed by severe gastrointestinal toxicity in the form of ulcers in mouth, mucositis, stomatitis, bleeding in the digestive tract. Also, the results of studies obtained in the U.S. in the '90s, indicated mucositis as the most frequent side effect of MTX in doses of 1 g/m^2, with absence of the antidote [9]. Our study showed that patients did not have any of the listed side effects, although higher doses of MTX were applied, along with Calcium Folinate.

The most frequent side effect that occurred in the patients involved in the study is bone marrow depression. A study of adverse effects of MTX at a dose of 3 g/m^2 found haematological toxicity as the most frequent side effect, which occurred in 87% of patients involved in research [10]. These side effects are expected and we can explain them by the mechanism of action of MTX, which inhibits the synthesis of folic acid and primarily acts on cells that divide rapidly, which include bone marrow cells. The average value and

standard deviation of the number of leukocytes in all 4 applications of MTX in all 10 patients indicate that the number of white blood cells also decreases after the application of Calcium Folinate. However, the antidote achieved better effect on platelets, which mainly increased in number. The decrease in the number of platelets did not require platelet transfusion. In all the patients, the state was balanced between the two doses of MTX, which happened in the following two weeks, without any additional therapy. This data signifies the effectiveness of the treatment with high doses of MTX and the use of Calcium Folinate, which did not lead to severe complications of the therapy [2, 11].

According to the literature, liver disorder is also one of the most frequent side effects of MTX [3]. Amongst these, elevated activity of enzymes aminotransaminases and lactate dehydrogenases occur most often, but the impairment of these parameters is reversible and does not lead to chronic liver disease [12]. Our results show that higher values of enzymes ALT, AST and GGT were found in two patients. These parameters indicate that the application of MTX induced hepatotoxicity. After the use of silymarin and ursodeoxycholic acid the liver enzyme activity has dropped to normal. The liver lesion was mild, so it was not necessary to discontinue the chemotherapy and silymarin has proven to be an effective drug in the prevention of liver complications after application of chemotherapeutic agents. When applied in lower doses, MTX induces less hepatotoxicity. Patients treated for rheumatoid arthritis or psoriasis, who received MTX at a dose of less than 2 g/m^2, had a lower incidence of hepatotoxicity [13]. That indicated that the higher doses are followed by the more severe adverse reactions.

Results of a clinical study that followed the response of the therapy with MTX (2 and 3 g/m^2) in the consolidation phase in children with ALL, indicated that nausea and vomiting usually occur immediately after treatment [14]. In our study there was no nausea and vomiting. However, as mentioned in the study, MTX was applied at a dose of 2 g/m^2. Granisetron, serotonin 5–HT3 receptor antagonist, was applied in both therapeutic protocols for the prevention of nausea and vomiting.

In one patient, after the use of MTX, there was a gastrointestinal intolerance in the form of diarrhoea with mild cramps. The symptoms have withdrawn after a short period with no need for additional therapy.

In three patients MTX caused fever, and one patient had developed an infectious complication in the form of bronchopneumonia. After empirical application of wide-range antibiotics and an antifungal drug, fluconazole, signs of bronchopneumonia withdrew. These side effects can be related to the fact that patients treated with cytotoxic drugs are prone to infections and fever due to bone marrow depression.

Metabolic toxicity was observed in one of the patients in the form of elevated calcium level for the short time period and did not require additional therapy. Other published data indicate that hypercalcaemia occurs in children with ALL, as one of the metabolic disorders due to elevated parathyroid hormone (PTH or polypeptide-related PTHrp) in malignant cells, leading to bone resorption and increased calcium levels [15].

Results of other studies have shown that MTX caused neurotoxic adverse effects in the form of subacute necrotizing encephalopathy and cerebral venous thrombosis after intrathecal administration, in the treatment of malignancies in pediatric age group [16]. In our study, no adverse effects occurred that would indicate damage to the central nervous system induced by the cytotoxic drug. The results of studies that followed neurotoxicity caused by MTX, state that this adverse effect occurs in 3-11% of patients, depending on the dose of MTX and Calcium Folinate. There is a connection between high-dose MTX and increased levels of MTX/Calcium Folinate with neurotoxic occurrence. This type of adverse action has lower incidence in the treatment of solid tumors, probably due to higher doses of antidote [6].

Adverse effects that occurred in the consolidation phase were of mild to moderate intensity (level 1 or 2) and did not lead to more severe complications of the treatment. This result complies with the results of other studies that also did not show any adverse effects of severe character. In one of the mentioned studies, MTX toxicity was observed at doses of 2 or 3 g/m^2, in 218 children with ALL. The intensity and frequency of side effects were observed using the form taken by the NCI-CTC, the same form that we used in our study. Adverse effects were of level 1 or 2 in the consolidation phase [14]. Nevertheless, the number of the patients involved in the study was limited due to low incidence of ALL in children population, but number of MTX administration (40) allowed us

to conclude about its efficacy and safety profile and possibilities to increase its tolerability.

The results of our study correspond with other studies. The most frequent side effects caused by the medium-high dose of MTX were leukopenia and thrombocytopenia. After the Calcium Folinate application, platelet number returned to normal values significantly sooner than the number of leukocytes.

CONCLUSIONS

The highest prophylactic effect of Calcium Folinate, applied to ALL BMF IC-2009 protocol, referred to the severe side effects of the gastrointestinal tract (ulcers, mucositis, stomatitis, gastrointestinal bleeding) induced by MTX, which were not observed in our study. Silymarin and ursodeoxycholic acid, significantly prevented severe liver function impairment. Adverse effects which occurred after the application of the medium-high dose of MTX were of mild to moderate intensity, and of reversible character. Due to the Calcium Folinate application, prevention of severe side effects and the quality of life in children with ALL are significantly improved.

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Transparency Declarations

Competing interests: none to declare.

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Uticaj preparata za detoksikaciju na intenzitet neželjenog dejstva umereno visokih doza metotreksata kod dece obolele od akutne limfoblastne leukemije: serija slučajeva

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KRATAK SADRŽAJ

Cilj rada U našoj zemlji se lečenje akutne limfoblastne leukemije (ALL) kod dece vrši prema protokolu ALL IC-BMF 2009. Terapija obuhvata primenu citostatika (metotreksata i 6-merkaptopurina) i leka za detoksikaciju (kalcijum-folinata). Danas se 80% dece s ovim oboljenjem izleči, međutim, rezistencija na primenjenu terapiju i njeno toksično dejstvo i dalje su ozbiljan klinički problem. Cilj rada je bio da se utvrde neželjena delovanja metotreksata kod dece obolele od ALL prema protokolu ALL IC-BMF 2009 i uloga kalcijum-folinata, silimarina i ursodeoksiholne kiseline u sprečavanju nastanka teških neželjenih posledica primene leka.

Metode rada Neželjena dejstva su utvrđena na osnovu modifikovanog obrasca za praćenje akutne toksičnosti terapije. Istraživanje je obuhvatilo desetoro dece sa ALL standardnog ili umerenog rizika u fazi konsolidacije koja su lečena od jula 2010. do februara 2011. godine u Institutu za zdravstvenu zaštitu dece i omladine Vojvodine u Novom Sadu.

Rezultati Najčešće neželjeno dejstvo koje se javilo posle 40 primenjenih doza leka kod bolesnika bila je depresija kostne srži. Metotreksat je izazvao leukopeniju kod svih deset bolesnika i trombocitopeniju kod petoro dece. Nakon primene kalcijum-folinata broj trombocita se povećao kod osmoro dece, a broj leukocita kod dva bolesnika. Ređa neželjena dejstva bila su: povišen nivo transaminaza, febrilno stanje, bronhopneumonija, dijareja sa slabim grčevima i hiperkalcemija.a

Zaključak Primena kalcijum-folinata, silimarina i ursodeoksiholne kiseline je sprečila pojavu težih neželjenih dejstava umereno visokih doza metotreksata kod dece sa ALL. Zapažena neželjena dejstva su bila blagog do umerenog intenziteta i reverzibilne prirode i nisu značajnije remetila kvalitet života ove obolele dece.

Ključne reči: akutna limfoblastna leukemija; metotreksat; kalcijum-folinat

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