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METOTREKSATIN TOKSİK TƏSİRLƏRİNİN TƏDQİQİ

T.V.Ryabenko, V.İ.Hula, O.V.Korenkov, A.A.Ponırko, T.P.Teslık, S.M.Dmitruk, V.Yu.İlyasenko, Y.S.Dudçenko
Sumı Dövlət Universitetinin Morfologiya kafedrası, Sumı, Ukrayna

Məqalədə müxtəlif xəstəliklərin müalicəsində tətbiq edilən metotreksatın toksik təsirinə dair ədəbiyyat məlumatları təhlil edilmiş, onların inkişafının qarşısını almağın elmi üsullarının analizi aparılmışdır.

Ədəbiyyat məlumatlarına görə metotreksatın toksik təsirləri qaraciyərin, böyrəklərin, ağciyərlərin, həzm sisteminin və dərinin zədələnmələri ilə təzahür edir; bu preparat aydın ifadəli embriotoksik və teratogen təsir effektinə malikdir. Qan göstəricilərinin monitorinqi və preparatın dozasının düzgün təyin edilməsi onun toksik təsirlərini minimuma endirməyə və əsas xəstəliyin müalicəsində uğur qazanmağa imkan verə bilər.

Açar sözlər: *metotreksat, toksiklik, yanaşı təsirlər*

Key words: *methotrexate, toxisity, side effects*

Ключевые слова: *метотрексат, токсичность, побочные эффекты*

EVALUATION OF METHOTREXATE TOXICITY

T.V.Riabenko, V.I.Hula, O.V.Korenkov, A.A.Ponyrko, T.P.Teslyk, S.M.Dmytruk, V.Yu.Illiashenko, Y.S.Dudchenko
Department of Morphology, Sumy State University, Sumy, Ukraine

The article analyzes literary sources on the study of the toxic effects of methotrexate in the treatment of various diseases and examines scientific data on methods of preventing their development.

According to the literary information, the main toxic effects of methotrexate manifest as damage to the liver, kidneys, bone marrow, lungs, digestive system, and skin. Methotrexate exhibits pronounced embryotoxic and teratogenic effects. Monitoring of blood test parameters and selection of an optimal dose will minimize methotrexate toxic effects and help in achieving success in the treatment.

INTRODUCTION

Methotrexate (MT) is widely used in medicine for the treatment of a large number of diseases, including cancer, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriasis, sarcoidosis, Crohn's disease, dermatomyositis, Wegener's granulomatosis, vasculitis, ectopic pregnancy and after organ transplantation [1,2,3]. The medication has cytotoxic, anti-inflammatory, and immunosuppressive effects [4].

MT belongs to antitumor chemotherapeutic agents, a group of antimetabolites. It is prescribed for the treatment of malignancies such as acute lymphoblastic leukemia, osteosarcoma, breast cancer, and non-Hodgkin's lymphoma [5]. According to the literary scientific sources, the mechanism of action of MT is due to the inhibition of the dihydrofolate reductase enzyme that, in turn, reduces the use of folates during purine and pyrimidine synthesis and disrupts DNA/RNA synthesis and cellular replication. The main effect of MT is aimed at the S-phase of cell mitosis; thus the agent is most effective with actively proliferating tissues, such as malignant cells, bone marrow, fetal cells, mucous membranes of the oral cavity and intestines, skin epithelium, and bladder cells. Because the proliferation of malignant cells is more intensive than that of most normal cells, MT can slow down malignant cell proliferation without causing irreversible damage to normal tissue [6]. In addition, the cytotoxic effect of the medication has been shown to occur when extremely high doses are prescribed (>1000 mg/m^2) [7].

Strazzulla L.C. reported that much smaller doses of MT reduce inflammation in tissues and joints due to the accumulation of folate-dependent enzymes in cells. This process causes the release of adenosine, which has a pronounced anti-inflammatory effect. Adenosine is a purine nucleoside produced extracellularly and intracellularly in response to stimuli such as inflammation and hypoxia. It interacts with receptors that play a key role in the osteoblast, osteoclast, and chondrocyte function and differentiation [8]. Due to this, MT is a first-line drug in the treatment of rheumatoid arthritis and is widely prescribed in ankylosing spondylitis [9].

Bedoui Y. et al. showed in their study that MT affects the synthesis of polyamines (spermine and spermidine) as a result of inhibiting the regeneration of methionine from homocysteine, which leads to further disruption of cell DNA methylation. MT also has an immunosuppressive effect, which is due to its ability to suppress the division of lymphocytes. Low doses of MT cause a decrease in the cytokines synthesized by alveolar macrophages and a delay in fibroblast proliferation [10].

According to the recommendations of rheumatologists, MT is prescribed as tablets or injections once a week. Patients take the necessary dose at once or divide it into 2 doses, administered within a 24-hour. Since the medication has a cumulative effect, its action is manifested after 1.5-2 months of administration. Dalix E. et al. discovered that a gradual dose increase during treatment prevents severe adverse reactions [11].

Study Objectives. The study aims to analyze the literary sources on methotrexate toxicity, methods of preventing their development, and recommendations for their treatment.

Materials and Methods. We performed an extended search and analysis of modern literary sources in the Web of Science, PubMed, and Scopus databases regarding MT toxic effects and methods of their prevention.

Results and Discussion. The main toxic effects of MT are damage to the liver, kidneys, bone marrow, lungs, and digestive system.

According to these literature sources, high blood levels of methotrexate are usually well tolerated for a short period. However, drug toxicity can occur after continuous exposure to high or low doses of methotrexate [12].

The main toxic effects of methotrexate are inhibition of bone marrow function, followed by bone marrow aging, and myelosuppression. Pountos I. and Giannoudis P.V. reported that decreased production of blood cells in the bone marrow could cause the development of infection, high temperature, lymphadenopathy, and bleeding [13]. According to Mori S. et al., myelosuppression usually occurs with long-term use of low doses of methotrexate (after one or two months). Hematological side effects of MT in patients manifested as leukopenia, neutropenia, thrombocytopenia, and anemia. No concomitant folic acid supplementation, simultaneous administration of several medication groups, and impaired kidney function contributed to the development of myelosuppression [14].

Mesenchymal stem cells are known to differentiate into osteoblasts, chondroblasts, and adipocytes. Bone marrow aging and myelosuppression with MT administration disrupt bone remodeling processes. Malakhov V.A. et al. have stated in the scientific works that the pro-inflammatory cytokines TNF-a, IL-1b, and IL-6 play a key role in osteoblastogenesis and osteoclastogenesis regulation. They can induce bone resorption, which activates osteoclastogenesis and causes bone loss [15]. This is confirmed by the research of Robin F. et al. suggesting that chemotherapy with methotrexate disrupts the process of bone remodeling and causes a decrease in the bone tissue mineral density due to a decreased number of osteoblasts, osteocytes, and chondrocytes in the growth plate and an increased number of osteoclasts. The mentioned changes determine the development of osteoporosis and are a prerequisite for bone fractures in the future [16].

A significant side effect of methotrexate therapy is liver toxicity. According to the results of research by Abe K. et al., the mechanism of MT hepatotoxicity is related to impaired purine synthesis, increased content of adenosine, and an imbalance in the content of cytokines. These changes are accompanied by oxidative imbalance in the liver and can lead to the development of liver steatosis, fibrosis, and cirrhosis during maintenance therapy with methotrexate, or hepatocellular carcinoma accompanied by fibrosis/cirrhosis [17]. These conclusions are confirmed by the scientific

works of Ezhilarasan D., suggesting that leukopenia and an increased level of transaminases (AlAT and AsAT) are the first signs of the toxic effect of MT. A moderate increase in ALT and AST levels occurred in 30% of patients receiving MT. The author demonstrated that dose reduction led to normalizing blood parameters without treatment withholding [18]. It should be noted that MT can't be prescribed to patients with a total bilirubin level > 85 μmol/l, as well as to patients with hepatitis B or C, or HIV. During the treatment with MT, it is necessary to measure transaminase levels every 6-8 weeks [19,20].

Treatment with methotrexate can have a toxic effect on the respiratory system. According to the scientific works of Fragoulis G.E. et al., this effect can manifest through methotrexate-induced interstitial lesions of the lungs, such as pneumonitis, interstitial pneumonia, pulmonary vasculitis, etc. [21]. This is confirmed by the study of Spagnolo P. et al., who reported dry cough, shortness of breath, and fever in inpatients. However, the researchers observed no X-ray changes in the lungs in the first weeks of the disease [22].

MT therapy requires careful monitoring of excretory system indicators, as the drug is metabolized in the liver and excreted by the kidneys within 48 hours. A study by Awad H. et al. revealed that the nephrotoxic effect of MT was associated with damage to the renal tubule epithelium, which led to impaired reabsorption [23]. This is consistent with the experimental study of Balowria K.S. et al., who found that methotrexate could cause postrenal toxic kidney damage in rats due to the precipitation of pharmaceutical substance crystals and the formation of urinary stones in the lumen of the distal tubules, which created mechanical obstacles to urine flow. Deposition of crystals in the parenchyma of the kidneys caused damage to the vascular network with consequent impairment of renal blood flow. This further promoted fibrosis and the development of an atrophic kidney [24]. Arakawa Y. reported that 2–12% of patients treated with MT might develop acute kidney injury leading to a delayed elimination of the drug and increased blood level of methotrexate. Therefore, methotrexate must be contraindicated in patients with kidney disorders [25].

The analysis of literature data reveals that MT can also cause a toxic effect on the gastrointestinal tract, such as inflammation of oral mucosa (ulcerative stomatitis, mucositis, gingivitis), nausea, diarrhea, and enteritis. However, Wang W. et al. investigated that these side effects were usually reversible and disappeared about two weeks after reducing the dose or increasing the interval between doses and adding folic acid supplements (calcium folinate, folic acid). However, it should be remembered that MT administration can lead to such dangerous complications as gastrointestinal bleeding and intestinal perforation, which can have fatal consequences [26].

An important factor in prescribing MT therapy is to inform patients of reproductive age about the necessity of birth control since the drug has a pronounced embryotoxic and teratogenic effect. According to the scientific research by Verberne E.A. et al., MT treatment might cause malformations of the facial skeleton, cardiovascular system, and limbs, such as microcephaly, craniosynostosis, tetralogy of Fallot, pulmonary valve atresia, limb reduction defects, and syndactyly [27]. Gutierrez J.C. and Hwang K. reported in their study that MT had not to be prescribed to men or women within three months before a planned pregnancy and to women during pregnancy and breastfeeding [28]. The scientists suggested that breastfeeding had to be contraindicated during MT therapy, as the substance could penetrate breast milk and cause child’s intoxication. According to the recommendations of Hannoodee M. et al., pregnancy should be planned no earlier than 6 months after the end of MT therapy [29].

Apart from that, Solomon D.H. et al. recommend informing patients that the long-term use of MT can possibly lead to the development of malignant diseases, in particular, hematological non-Hodgkin's lymphoma [30], the mechanism of which is poorly understood today.

According to the latest literary data, scientists report the toxic effect of MT on the central nervous system (neurotoxicity). Research results of Mateos M.K. and co-authors testified that 3-7% of children treated for acute lymphoblastic leukemia with high doses of MT experienced this type of complication, which was clinically manifested by convulsions,

stroke-like symptoms, speech disorders, and encephalopathy. The authors noted that such patients later had an increased risk of developing epilepsy [31]. Chen Y.C. et al. conducted a study on rats, which were administered MT, and reported the development of cognitive impairment caused by myelin loss through a direct effect on the myelination process or through epigenetic regulation of neurotrophin associated with myelination. Also, the neurotoxicity of MT was most often manifested as spatial memory impairment due to the effect of the chemotherapeutic agent on the hippocampus [32]. However, additional doses of folic acid (leucovorin) given in 24–36 hours after MT administration, according to the study by Cohen I.J., helped to reduce the neurotoxicity of the drug without violating the therapeutic outcome [33].

Methotrexate therapy can also cause the development of skin lesions. This is evidenced by the research by Zuber M. et al., who found that MT therapy in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriasis was often accompanied by toxic epidermal necrolysis, maculopapular rash, vasculitis, ulcerative psoriatic plaques, erythema multiforme, Stevens-Johnson syndrome, and photosensitive dermatitis. Immediate withdrawal of methotrexate plus folic acid supplementation and topical anti-inflammatory steroids were effective in treating methotrexate-related skin manifestations [34].

According to Friedman B. and Cronstein B., minor toxic effects, such as stomatitis, nausea, diarrhea, myalgia, alopecia, occur in 20–30% of patients. It was established that they resolved after dose reduction. Also, folic acid supplementation at a dose of 5 mg once a week or 1 mg a day in 48 hours after MT administration prevented these complications. The main toxic effects of MT in the form of liver, kidney, lung, and bone marrow disorders are less common, but may be life-threatening [35].

According to the recommendations of rheumatology experts, in particular Valerio V. and co-authors, severe kidney disease with a glomerular filtration rate of less than 30 mL/min, liver disease, leukocytopenia with less than 3.0×10^9/L, thrombocytopenia with less than 50×10^9/L, inadequate contraception, pregnancy, history of drug or alcohol abuse, acute or chronic infection, and lung disease are contraindications for MT treatment [36].

Conclusions:

A detailed analysis of current scientific data on the effect of MT as a part of complex chemotherapy on the organs and systems of the body revealed that the agent could cause damage to the liver, kidneys, bone marrow, lungs, skin, and digestive and nervous systems. Methotrexate has a pronounced embryotoxic and teratogenic effect.

MT treatment requires constant monitoring to reduce the risk of side effects. Before starting treatment, it is recommended to perform a chest X-ray examination, complete blood count, and blood chemistry, including creatinine, transaminase, bilirubin, and alkaline phosphatase levels, as well as serological tests for hepatitis B/C, HIV. Regular blood tests are obligatory during the treatment with MT. Measuring AST, ALT, and white cell count in the blood every 4 weeks is advisable.

Thus, MT has a toxic effect on all cells of the body, but monitoring of blood test parameters and selection of an optimal dose will minimize methotrexate toxicity and help in achieving success in the treatment.

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ИССЛЕДОВАНИЕ ТОКСИЧЕСКИХ ЭФФЕКТОВ МЕТОТРЕКСАТА

Т.В.Рябенко, В.И.Гула, А.В.Кореньков, А.А.Понырко, Т.П.Теслык, С.Н.Дмитрук, В.Ю.Ильяшенко, Е.С.Дудченко

Кафедра морфологии Сумского государственного университета, Сумы, Украина

В статье представлены литературные сведения с целью проанализировать научные исследования по изучению токсических эффектов метотрексата при лечении различных заболеваний, провести анализ научных данных методов предупреждения их развития.

Анализ литературных источников показал, что основные токсические эффекты метотрексата проявляются повреждением печени, почек, костного мозга, легких, пищеварительной системы и кожи. Метотрексат оказывает выраженное эмбриотоксическое и тератогенное действие. По мнению авторов мониторинг лабораторных показателей крови и правильно подобранная доза препарата может минимизировать его токсические эффекты и добиться успеха при лечении основного заболевания.

Author for correspondence:
Tetiana Riabenko – Assistant of the Department of Morphology, Sumy State University, Sumy, Ukraine
ORCID: 0000-0003-2740-389X
E-mail: t.riabenko@med.sumdu.edu.ua