IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

METHOTREXATE SIDE EFFECTS, PREVENTION AND TREATMENT

[1]Prajakta M. Kharole, [2]Umesh R. Bansod, [3]Neha L. Zod, [4]Nikita V. Mahalle
[1]Student, [2]Professor, [3]Professor, [4]Professor,
Dr. Rajendra Gode College Of Pharmacy, Amravati, Maharashtra – 444602, India

ABSTRACT: Methotrextae (MTX) is an antifolate first developed to treat certain types of cancer. It was used at higher doses as a cancer therapy and since 1990 it is used at much lower doses to treat rheumatic diseases [1]. Side effects of MTX high dose (MTX-HD) may be life threatening, however those of various doses of oral MTX are variable because of the interindividual variability of gastrointestinal absorption of this drug. Bone marrow, gastrointestinal mucosa and hair are particularly vulnerable to the effects of MTX, secondary to their high rate of cellular turnover [2] and because MTX concentration is inversly proportianal to renal clearance [2], renal toxicity is frequent with MTX-HD. This review is aimed at exposing MTX toxicity in different organs, at explaining pathogenic mechanisms of these toxicities and their prevention or treatment.

KEYWORDS : Methothexate, Toxicity, Side effects, Prevention.

INTRODUCTION : Methotrexate (MTX) is an antifolate first developed to treat certain types of cancer. It was used at higher doses as a cancer therapy and since 1990 it is used at much lower doses to treat rheumatic disease. Methotrexate is a useful antimetabolite for the treatment of both benign and malignant proliferative disorders. When the pharmacokinetics and potential toxicity of this drug are understood, treatment regimens can be tailored to the underlying kinetics of the target population.

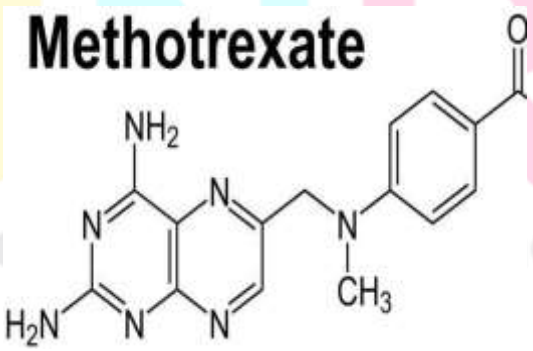


Fig. No. 1. Methotrexate

Renal Toxicity : Acute renal failure due to acute tubular necrosis induced by MTXHD is rare à 4%) but serious and redoubtable. This toxicity is due to the precipitation of MTX or its metabolites in the renal tubules causing obstruction and diminition of renal clearance with consequently prolongation of MTX high levels. High MTX levels may in turn lead to ineffective rescue by leucoverin and an enhancement of MTX's other toxicities

MTX may also acts as a direct toxin on the tubular epithelium and causes vasoconstriction of the afferent arteriole

The effect of high-dose methotrexate (MTX) administration on glomerular filtration rate was determined by pre- and posttreatment inulin and creatinine clearances in nine patients. MTX and its metabolites are relatively insoluble in acid urine . An increase in the urine pH results on a greater solubility of the MTX and its metabolites. For that reason, it is recommended to monitor renal function before, during and after MTX infusion in order to control its plsamtic levels. Intravenous hydratation and urine alkalinization were made before, during and after the infusion of MTX-HD . Clinically, patients with acute renal failure are usually asymptomatic. It consists frequently on a nonoliguric renal failure which generally disappears in two to three weeks.

High dose methotrexate (HDMTX) induced renal failure is a medical emergency, as methotrexate (MTX) is primarily eliminated by renal excretion. High doses of leucovorin (LV) do not necessarily prevent toxicity in the presence of sustained elevated plasma MTX concentrations. The bacterial enzyme carboxypeptidase-G2 (CPDG2) hydrolyzes MTX into inactive metabolites and has been demonstrated to lower plasma MTX concentrations to nontoxic levels rapidly in the nonhuman primate after HDMTX infusion. Therefore, CPDG2 was evaluated as a rescue agent in a patient with acute renal dysfunction secondary to HDMTX. High-dose methotrexate (HDMTX)-induced renal dysfunction can be life threatening, because it delays methotrexate (MTX) excretion, thereby exacerbating the other toxicities. MTX and its metabolites are relatively insoluble in acid urine . An increase in the urine pH results on a greater solubility of the MTX and its metabolites.

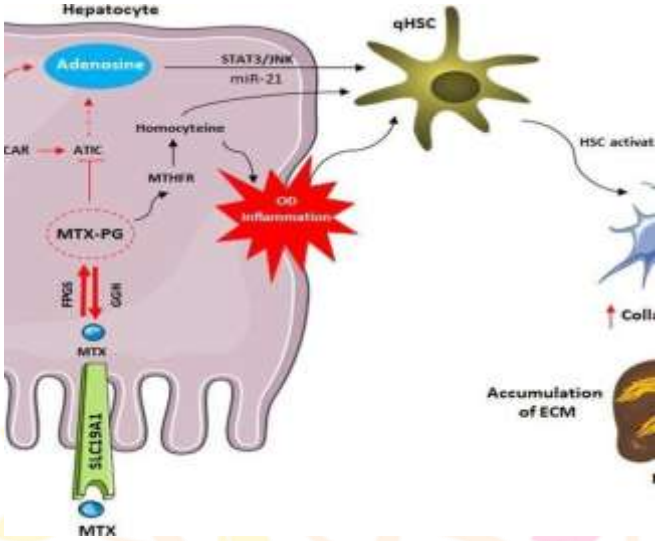
Neurotoxicity: MTX can induce acute, subacute or chronic neurotoxicity. This toxicity is mainly observed after intrathecal or intravenous administration of MTX [22-24]. Mechanisms of toxicity are not yet fully known but many hypotheses may explain this neurotoxicity, such as interference of MTX with transmethylation reactions which are important for the formation of proteins, lipids and myelin [25]. MTX decreases also the rate of methionine and S-
adenosyl methionine in cerebrospinal fluid and increases levels of S-adenosyl homocysteine and homocysteine. Methotrexate, a mainstay treatment for children with acute lymphoblastic leukaemia, can cause neurotoxicity, with paralysis, seizures, somnolence, anorexia, and headaches.

Since adenosine is a central nervous system depressant, we wondered whether adenosine release in the central nervous system could account for some of the neurotoxicity due to methotrexate, and whether that
toxicity could be lessened by displacement of adenosine from its
receptor by aminophylline. Chronic neurotoxicity is observed several months to years after MTX therapy. It is an irreversible complication and it is observed especially if an encephalic radiotherapy was associated to the therapeutic protocol . Necrotic leucoencephalopathy is the most frequent complication characterised by a slow progressive cognitive deterioration, seizures, ataxia, spasticity and/or coma MTX neurotoxicity is usually treated with aminophylline or leucoverin administration .

Hematologic Toxicity: Hematologic toxicity is a serious complication commonly observed with MTX-HD . This complication consists of a thrombocytopenia followed by a rapidly progressive leukoneutropenia . Leukopenia occurs from one to three weeks and marrow recovery is generally
observed within approximately 3 weeks . Hematologic toxicity including thrombocytopenia, megaloblastic anemia, leukopenia and pancytopenia with MTX low doses are rare . Their prevalence is about 3% in patients with
rheumatoid arthritis treated by MTX and the incidence of pancytopenia in these subjects is approximatively 1.4% . The frequency of pancytopenia may increase with co-administration of other drugs, folic acid deficiency,
hypoalbumenia, concomitant infections, advanced age, dehydratation and renal impairment . Pathogenesis of MTX inducing panctopenia is unclear.

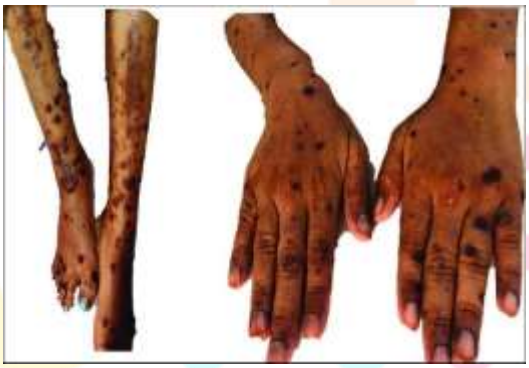
Pancytopenia may be acute or chronic and thought to be an allergy-like reaction. MTX-treated RA patients can have hematological damage, including myelosuppression, leukopenia, neutropenia, and
megaloblastic anemia . Furthermore, hematological toxicities result in up to 25% of people discontinuing treatment due to the risk of

mortality. Pancytopenia is among MTX toxicities and is difficult to prevent since it can appear unexpectedly during therapy . Although the actual mechanism of MTX-induced hematological toxicity is unknown, it has been connected to the genesis of RA. One source of MTX-induced hematopoietic toxicity has been identified as excess unbound extracellular MTX.



Cutaneomucus Toxicity: MTX has a variety of cutaneous side effects, particularly when it is administered at high doses. It generally occurs when recommended guidelines are ignored or renal excretion is decreased.

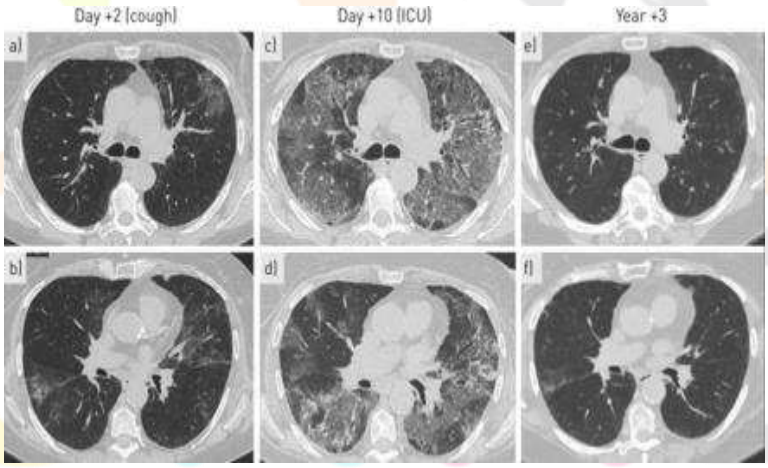
The most frequent mucocutaneous reactions to MTX are ulcerations of the oral mucosa, burning sensation of the skin, photosensitivity, acral erythema,
multiform erythema, urticaria and vasculitis [46]. The pathogenesis of skin adverse reactions due to MTX is not well known. Skin reactions to MTX-HD seem to be due to a cytotoxic-T lymphocytes and mononuclear cells that
induce apoptosis in keratinocytes expressing drug-derived antigens at their surfaces [47,48]. Hypersensitivity reactions may also explain some cutaneous side effects.



Gastro-Intestinal Toxicity: MTX can induce a variety of gastro-intestinal disorder. Patients usually present abdominal pain, vomiting and diarrehea.
These side effects may occur either with high or low MTX doses. t can affect the entire digestive system and is often accompanied by nausea,
stomach pain, and cramping. These symptoms often lead to
malabsorption, weight loss, and interruption of medications. Previous research in 1989 found that 20% to 70% of patients with RA reported gastrointestinal adverse effects within the first two years of
medication. These gastrointestinal adverse effects are the most
common side effects associated with MTX therapy . In a 2014 report, it was revealed that gastrointestinal complaints, such as vomiting, nausea, diarrhea, anorexia, and abdominal distress, were observed

frequently . In addition, a study discovered a higher incidence of diarrhea in RA patients who receive oral MTX medication.

Pulmonary Toxicity: Pneumonitis is one of the most serious but
infrequent side effects of MTX low doses. Its prevalence seems about 0.9 to 1% [58,59]. Mechanism of pneumonitis is an hypersensitivity reaction to MTX
mediated by activated T-cells. According to one study, more than 25% of patients who receive MTX treatment have coughing, wheezing,
breathlessness, or other respiratory problems . Research published in 2014 found that MTX therapy increases the risk of lung disease in patients compared to other DMARDs . A 2009 study discovered that MTX causes lung damage due to cytokine release . Individuals may
have respiratory side effects after four weeks of starting MTX, which are likely to be caused by idiosyncratic immunological responses .
Fibrosis, interstitial pneumonitis, or even substantial alveolar
destruction may be the result of MTX-induced respiratory toxicity. A patient treated with 7.5 mg methotrexate/week (MTX) for rheumatoid arthritis (total dose 300 mg) developed high fever, dry cough and progressive dyspnea and hypoxemia due to a severe interstitial
pneumonitis. MTX was discontinued and an infectious etiology was ruled out by cultures, serology and lung biopsy. Corticosteroids administered intravenously in high dose led to a dramatic improvement and a
complete amelioration of all symptoms and signs. Pulmonary toxicity is a rare adverse effect of low dose MTX therapy and a review of the
literature reveals 6 additional cases. Long-term MTX therapy was shown to cause alveolar epithelial cell damage and lung fibrosis in an animal model . According to case-control studies, several risk factors have been proposed, including rheumatoid pleuropulmonary involvement, old age, diabetes, hypovolemia, and previous use of DMARDs . These respiratory adverse effects might be associated with rheumatoid symptoms. As a consequence, RA patients receiving MTX should be
continuously monitored in the event of respiratory symptoms.



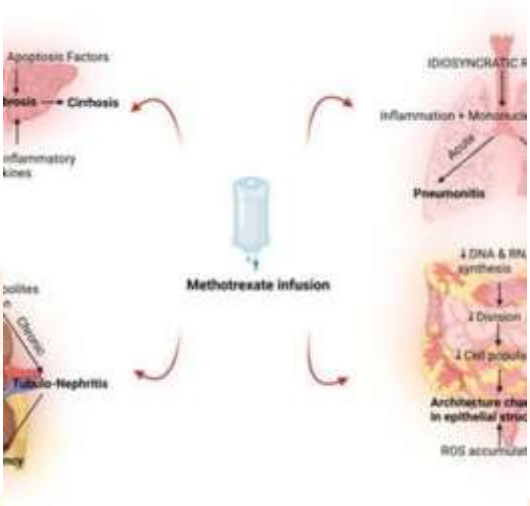
Dermatological Toxicity: MTX is an anti-inflammatory medication used to cure psoriasis . Its toxicity is rare given low doses, a proper dose schedule, and adherence to guidelines . MTX may still induce dermatological toxicity. The dermatological adverse effects of MTX treatment range from minor to severe. MTX toxicity may appear

as bone marrow suppression and gastrointestinal ulcers. Other unusual but often observed characteristics include cutaneous ulceration within skin lesions in individuals with underlying psoriasis vulgaris. Before starting MTX treatment, a viable pregnancy must be avoided, and kidney and liver function tests and liver enzymes, as well as a complete blood count, must be performed. A complete blood

count must be obtained seven days after starting MTX as well as after subsequent dosage increases. Blood counts should be checked every two to four weeks for the first few months . MTX's toxic effects must be treated early. Dermatologists must detect clinical and
histopathological poisoning. The characteristic histology of cutaneous MTX toxicity, including keratinocyte enlargement and epidermal necrolysis, confirms clinical observations of direct toxic action.

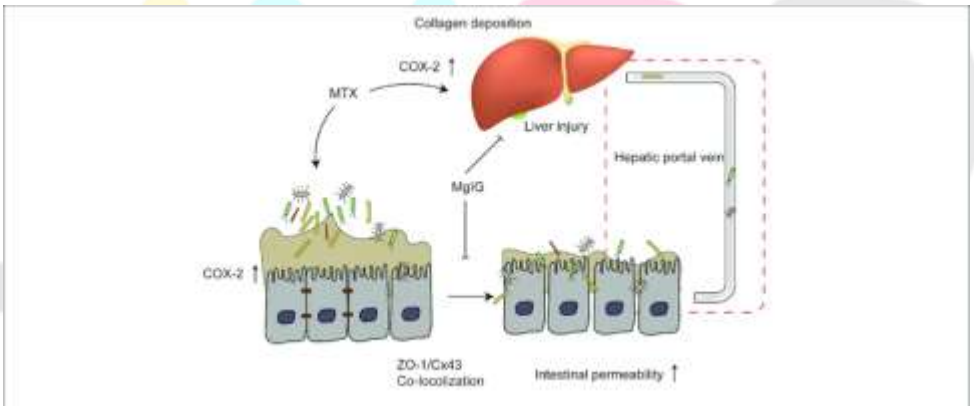
Dermatological side effects, such as nonspecific morbilliform drug rashes, which are erythematous, macular, itchy, and limited to the neck and trunk, are reported to affect 14% to 15% of people.

Liver Toxicity: A study from 1971 found altered liver functions in patients when using MTX



to treat psoriasis. A study from 1989
reported that hepatotoxicity in patients with RA could reach 70% during the first two to four years of MTX treatment . Research in 2010 discovered that increased liver enzymes, notably alanine

aminotransferase and aspartate aminotransferase, were associated with MTX . The method by which MTX induces hepatotoxicity has not yet been determined; however, it is thought to be connected to the cellular pathways of the drug . There are various possibilities, one of which is that MTX activates Ito cells in the liver . When Ito cells are
triggered by prolonged liver damage, they shift to myofibroblasts, which are producers of collagen and other matrix proteins, such as fibronectin, resulting in cell enlargement.



Prevention and Management OF Methotrexate High Dose Toxicity:

To avoid MTX toxicity, there are some general aspects of MTX-HD
administration and post-treatment management that are common to all regimens.

Methotrexate (MTX) is one of the most widely used anti-cancer agents, and administration of high-dose methotrexate (HDMTX) followed by leucovorin (LV) rescue is an important component in the treatment of a variety of childhood and adult cancers. HDMTX can be safely
administered to patients with normal renal function by the use of alkalinization, hydration, and pharmacokinetically guided LV rescue.

Despite these measures, HDMTX-induced renal dysfunction continues to occur in approximately 1.8% of patients with osteosarcoma treated on
clinical trials.

High-dose methotrexate (HDMTX), defined as a dose higher than 500 mg/m^2, is used to treat a range of adult and childhood cancers. The addition of methotrexate to treatment protocols in children with acute lymphoblastic leukemia has been found beneficial in preventing central nervous system relapse. Methotrexate is administered at doses that range from 12 mg intrathecally and 20 mg/m^2 orally, intramuscularly, or intravenously as weekly maintenance chemotherapy for ALL to
doses as high as 33,000 mg/m^2 intravenously for some other indications . Doses of 500 mg/m^2 or higher given intravenously are defined as high-dose methotrexate (HDMTX) and are used to treat a variety of adult and pediatric cancers, including ALL, osteosarcoma, and lymphomas . HDMTX therapy can cause significant toxicity, which not only leads to morbidity and occasional mortality but may also interrupt cancer treatment, potentially leading to inferior anticancer outcomes. To prevent unacceptable toxicity, it must be given with rigorously standardized supportive care , which differs across tumor types and treatment protocols . When patients experience delayed methotrexate excretion, without timely recognition and treatment, the prolonged exposure to toxic methotrexate concentration can lead to significant morbidity and mortality.

Maintaining adequate hydratation :Agressive hydration is important to promote diuresis and to prevent intratubular precipitation of MTX. Most protocols recommend at least 2.5 to 3.5 L/m2 of IV fluid hydration per day, starting 4 to 12 hours prior to the
initiation of the MTX infusion.

Avoiding drug interactions: Toxicity with MTX-HD may be increased when there is coadministartion of drugs having the potentiel to displace MTX from serum proteins and/or to reduce MTX clearance. The most known are interaction with trimethoprim and sulfamethoxazole (TMP-SMX) and non steroidal anti-inflammatory drugs (NSAID) . Alteration of the elimination of MTX was also reported with pyrazoles, aminoglycosides,
probenecid, some penicillins and macrolides , omeprazole.

Conclusion: Because MTX can cause many side effects and some of them are life threatening, it is important to recognize them as the drug must be discontinued immediately and rescue measures instituted. Many of these side effects can be avoided by a close monitoring and a good Prevention.

References :

1. Benedek TG (2010) Methotrexate: from its introduction to non-oncologic therapeutics to anti-TNF.

Clin Exp Rheumatol 28:

2. Widemann BC, Adamson PC (2006) Understanding and managing methotrexate nephrotoxicity. Oncologist 11:

3. Stark AN, Jackson G, Carey PJ, Arfeen S, Proctor SJ (1989) Severe renal toxicity due to intermediate-dose methotrexate. Cancer Chemother Pharmacol.

4. Shuper A, Stark B, Kornreich L, Cohen IJ, Avrahami G, et al. (2002) Methotrexate-related neurotoxicity in the treatment of childhood acute lymphoblastic leukemia. Isr Med Assoc J 4: 1050- 1053.

5. Weiss HD, Walker MD, Wiernik PH (1974) Neurotoxicity of commonly used antineoplastic agents (first oftwo parts). N Engl J Med 291: 75-81.

6. The hepatic stellate[Ito]cell:its role in human liver disease.HautekeeteML,GeertsA.Virchows Arch.1997;430;195-207

7. Desouza C,Keebler M,McNamara DB,FonsecaV.Drugs.

8. Curtis jR,Beukelman T, Onofrei A,et al.Ann Rheum dis.2010;69;43-47

9. Mckendry RJ.Aech Intern Med.

10. Dahi MG,Greory MM,Scheuer PJ, Br Med j.

11. Kalb RE,Strober B, Weinstein G,Lebwohl M.J mAm Acad Dermatol.

12. Truchuelo T, Alcantara J,Moreno c,Vano-Galvan S,Jaen P. 13.Morgan SL,Baggott JE,Vaughn WH,et al.Ann Intern Med . 14.Olsen EA.J Am Acad Dermatol.1991;25:306-318.

13. Solomon DH,Glynn RJ,Karlson EW,et al.Ann Intern Med. 16.Elsasser s,dalquen P, Soler M,Perruchoud AP.

14. Preventing and Managing Toxicities of high dose MTX:Scott C Howard ,John McCormick ,Ching-Hon Pui,Randall K buddington.

15. Brigitte C Widemann ,Peter C Adamson.