Methotrexate Toxicity: Molecular Mechanisms and Management

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i49B33357

Editor(s):

(1) Dr. Ana Cláudia Coelho, University of Trás-os-Montes and Alto Douro, Portugal.

Reviewer(s):

(1) Amal Halim, Mansoura University, Egypt.
(2) Swapan Kumar Chatterjee, India.

Complete Peer review History: https://www.sdiarticle4.com/review-history/76915

Received 06 September 2021
Accepted 10 November 2021
Published 12 November 2021

ABSTRACT

Methotrexate (MTX) is the most widely used drug in cancer chemotherapy and is considered to be the first-line drug for the treatment of a number of rheumatic and non-rheumatic disorders. The pulmonary toxicity, hepatotoxicity of MTX are two of its major side effects. Other toxicities such as endocrinological toxicity, GI toxicity, cutaneous toxicity, hematological toxicity, fatal malfunction or loss, and malignancy can also occur, but at a significantly lower rate of prevalence. This review aims to provide a comprehensive understanding of the molecular mechanisms of methotrexate toxic effects and Lastly, we discussed the management of this toxicity.

Keywords: Methotrexate; Methotrexate toxicity; Rheumatoid Arthritis; Organ toxicity; Mechanism of methotrexate toxicity; Management of methotrexate-induced toxicity; hepatotoxicity; pulmonary toxicity.

1. INTRODUCTION

1.1 Overview of Methotrexate

4-amino-10-methylfolic acid, also referred to as methotrexate (MTX), acts as a folic acid analogue and antagonist. It is generally employed for the therapy of a spectrum of neoplastic and non-neoplastic pathologies [1]. Initially, MTX was utilised as an anti-tumour agent. Currently, it is one of the principal
disease-modifying anti-rheumatic drugs (DMARDs) indicated for conditions, such as psoriatic skin disorders, rheumatoid arthritis (RA) and juvenile idiopathic arthritis. Additionally, it is a useful agent for the management of inflammatory bowel disorders, multiple sclerosis, vasculitic conditions and connective tissue pathologies, such as systemic lupus erythematosus, amongst others. In addition, its valuable anti-inflammatory and immunomodulatory features are important components of transplantations [1–3].

The treatment of viral mediated arthritis has received increasing attention due to MTX [4]. The multiple viruses associated with inflammatory joint pathologies encompass Old World alphaviruses, parvovirus B19, hepatitis B (HBV) and C (HVC), respectively, and human immunodeficiency virus (HIV) [5]. From a clinical perspective, ongoing viral-induced joint inflammation can mimic RA, and be present for periods of months to years [6]. In view of the comparable disease processes underlying RA and viral arthritides, MTX may of value in the treatment of the latter. However, an important factor that should not be disregarded is the possible risk of compromising patients’ immune surveillance to avert viral reactivation [7]. The World Health Organisation (WHO) deem MTX a vital medication. Undeniably, it is one of the most significant pharmaceutical advancements as it identified indications that differ substantially from its initial purpose [8,9].

Numerous advantageous biological compounds have entered the clinical arena as therapeutic agents for autoimmune inflammatory pathologies, e.g. RA. However, MTX is well-established as highly efficacious; it is a commonly used treatment which is often used as a benchmark against which to compare the performance of de novo DMARDs [1]. As a single agent, MTX can be employed as the initial drug of choice in individuals who have not previously received DMARDs [10]. Additionally, it can be utilised as an anchor agent in individuals who have had an insufficient reaction to MTX, together with additional characteristic or biological DMARDS in order to enhance disease control [11,12]. In the case of inflammatory diseases, MTX is administered in less frequent and lower doses. To compare, treating malignancy entails 5g per week doses, whereas for RA, the most effectual clinical results are observed after 10-25mg once per week doses of MTX. This represents the most typical indication for low-dose MTX usage [19]. The essential pathways that underlie the beneficial effect of larger doses of MTX on neoplastic pathologies are well-known. In its capacity as an antagonist to folic acid, MTX inhibits the function of enzymes reliant on folate, and therefore the manufacture of purine and pyrimidine essential for the generation of nuclear material that is rapidly replicated within tumour cell lines [14].

However, there is less clarity regarding the effect of the mechanisms involved in low doses of MTX in inflammatory disorders. Whilst MTX is recognised as being very cost-effective with strong efficacy/toxicity ratios, toxicity nevertheless remains an issue. Attention has been drawn to the possible adverse incidents associated with MTX as they reflect the main reason for its cessation [15–16]. Although it is widely utilised in the treatment of a range of autoimmune and inflammatory disorders, there is still drug toxicity associated with low dose MTX. The most frequently arising adverse events associated with MTX are principally related to the digestive tract, e.g. nausea, vomiting, oral inflammation, anorexia and liver damage [17]. Typically, toxicity rather than ineffectiveness is the primary cause of MTX treatment withdrawal [17]. Thus, periodic, meticulous, and suitable patient monitoring is critical and evidently substantially decreases the risks related to MTX usage [18]. The pathways underlying the toxic consequences of MTX have not been fully delineated. Some effects, such as diminished cell counts, digestive issues and oral inflammation are related to folic acid lack; complementary folic acid or folinic acid may resolve such manifestations [19]. Adverse events that are unconnected to its effect on folic acid encompass the presence of nodules, lung fibrosis, apathy, exhaustion and kidney dysfunction [14]. A more in-depth comprehension of MTX’s molecular mechanisms may aid in clarifying numerous toxicities related to MTX [14].

2. HEPATOTOXICITY

2.1 Molecular Pathways Underlying Hepatotoxicity Related to MTX Administration

There are two routes through which MTX can gain access to liver cells. These are via the folate transporter, i.e. solute carrier family 19, member 1, and via reduced folate carrier 1 [20]. Within the liver cells, MTX is converted into MXT polyglutamates (MTX-PGs), a process catalysed
by the enzyme, folylpolyglutamate synthetase (FPGS). Glutamate is concurrently eradicated from MTX-PGs via gamma-glutamyl hydrolase activity, which reverts them back to MTX [21].

Adenosine triphosphate (ATP)-binding cassette transporter A1 eliminates the glutamate-free MTX from the hepatocytes [21]. MTX-PGs stay present within the target cells for a considerable time period, during which they trigger a spectrum of disease-inducing pathways linked to inflammatory processes, oxidative stress, fibrosis and programmed cell death within the cell. Hence, the exploration of MTX-generated toxicities necessitates monitoring the level of MTX-PG [22]. Basic research has emphasized the likelihood that MTX may precipitate oxidative stress within hepatic tissue. In the liver tissue, the inception of intracellular oxidative stress suggests the MTX-PGs metabolite. As previously discussed, there has been empirical and clinical verification of the elevation of serum transaminases (AST and ALT) following the administration of MTX [23-26]. Moreover, as indicated by previous research, its MTX-PG metabolites induced lipid peroxidation signifies that the elevation of hepatotoxicity’s marker enzymes can be connected to MTX-induced hepatocellular degeneration. The breakdown products from MTX-PGS initiate lipid peroxidation which liberates ROS, NO and additional free radicals; these lead to cytoplasmic antioxidant downregulation, which includes both enzymes and non-enzymatic compounds, such as SOD, CAT, GSH and GPx [24-27].

The reduction in intracellular antioxidants may reflect their excessive engagement with the surplus generation of free radicals arising from intracellular MTX-PGs. The latter lead to the breakdown of liver cell membranes, with the consequent liberation of cytoplasmic components into the extracellular matrix. This may be the immediate reason for raised serum titres of AST and ALT associated with MTX. ARE, i.e. a cis-acting enhancer sequence, and whose locus is within the gene promotor region responsible for detoxification enzyme decoding, functions to diminish oxidative stress within the cell, mediating transcriptional stimulation in genes that govern antioxidant operations [28]. The redox equilibrium within the cell is moderated by ARE-linked genes, i.e. Nrf2, HO-1 and NQO1 [29-31]. It has been demonstrated that ARE is restricted by intracellular ROS which are derived from MTX-PGs; these are additionally responsible for the downregulation of oxidant resistant mediators, e.g. Nrf2, HO-1 and NQO1 [32-35]. These studies also highlight MTX’s oxidative stress-inducing potential in the tissue of the liver. NF-kB, JNK and JAK (Janus kinase)-STAT-3 signalling cascades may also be initiated during the inflammatory response [36]. Intracellular ROS are triggered by MTX-PG which, in turn, activates transcription factors, e.g. NF-kB and Nrf-2. A pro-inflammatory response is instigated via their nuclear translocation and the liberation of multiple enzymes and cytokines related to the inflammatory process, such as COX-2, NOS, TNF-α, IL-1β, 6 and 12 [37-38].

Typically, advancement to hepatic fibrosis is induced by continual liver inflammation [39]. Following damage to the liver, injured hepatocytes discharge diverse pro-inflammatory markers, which convert inactive HSCs to an active state or generate phenotypes akin to myofibroblasts (MFBs). The triggered HSCs give rise to the marked production of the extracellular matrix that generates liver fibrosis [40-41]. Furthermore, the accrual of MTX-PG within the liver tissue stimulates MTHFR, which, in turn, precipitates raised titres of intracellular and serum homocysteine [42-43]. There is an association between the accumulation of intracellular homocysteine levels generated by MTX-PGs and the progression of hepatic oxidative stress, and inflammatory and fibrotic processes [44-45]. Oxidative stress is a major pathogenetic mechanism for the latter [46] qHSCs are stimulated within the peri-sinusoidal space as a consequence of the MTX-PG-induced ROS synthesis and subsequent oxidative stress; a stimulated MFBs-like phenotype is thus exhibited. This gives rise to the heightened extracellular matrix manufacture and liver tissue fibrosis. The ATIC enzyme, which converts AICAR to formyl AICAR, is inhibited by MTX-PG. Additionally, MTX-PG obstructs DHFR, which is a catalyst for the decrease of dihydrofolate to tetrahydrofolate. It constrains thymidylate synthetase, which causes thymidine residues to form. Thus, the accrual of adenosine within the cell is a function of the MTX-PGs. This then activates the fibrotic process via collagen manufacture amplification and matrix-degrading matrix metalloproteinase (MMP) downregulation (Fig. 1).

The demise of liver cells reflects the diminution of liver folate concentrations and the manufacture of nuclear material within the cells as a result of the activities of MTX-PGs [47-48].
Programmed cell death of liver cells is a recognised outcome associated with DILI [49]. Caspase 3 expression is amplified by MTX; this initiates the intrahepatocytic apoptotic pathway, thus leading to cellular demise [50]. The equilibrium of pro- (bcl2) and anti- (bax) apoptotic indicators is altered by MTX-induced proinflammatory indicators [51].

The mitochondria operate as the source of ROS and their target concurrently. MTX has been demonstrated to stimulate hepatic steatosis, a process which arises via the mitochondrial respiratory chain and mitigation of the oxidation of fatty acids. Surplus ROS within the cell can alter the membrane potential of the mitochondria (ΔΨm) [52]. Following administration of MTX in liver tissue, both ROS-mediated mitochondrial toxicity and ΔΨm dispersion were observed [53]. The changes in bax and bcl-2 equilibrium together with ΔΨm attrition initiated by MTX-PG can lead to the liberation of cytochrome c from the mitochondria into the cytoplasmic matrix. Here, apoptosomes are generated from cytochrome c, which synthesise caspase 3; this enzyme triggers programmed liver cell death. The ways in which MTX can induce liver toxicity are illustrated in Fig. 2.

![Fig. 1. Potential pathways underlying liver fibrosis associated with methotrexate (MTX). ATIC, 5-aminomidazole-4-carboxamide ribonucleotide (AICAR) transformylase; FAICAR, 5-formamidoimidazole-4-carboxamide ribonucleotide; MTX-PG, MTX- polyglutamates; FPGS, folylpolyglutamate synthetase; GGH, gamma-glutamyl hydrolase; SLC19A1, solute Carrier Family 19 Member 1; qHSC, quiescent HSC; MFB, myofibroblast; MMP, matrix metalloproteinases; ECM, extracellular matrix; MTHFR, Methylenetetrahydro folate reductase; OD, oxidative stress; STAT3, signal transducer and activator of transcription 3; JNK, c-Jun N-terminal kinases. Adopted from [42]](image)
Fig. 2. Pathways underlying liver toxicity associated with methotrexate (MTX). SLC19A1, solute Carrier Family 19 Member 1; ATIC, 5-aminomimidazole-4-carboxamide ribonucleotide (AICAR) transformylase; FAICAR, 5-formamidomimidazole-4-carboxamide ribonucleotide; MTX-PG, MTX- polyglutamates; FPGS, folylpolyglutamate synthetase; GGH, gamma-glutamyl hydrolase; qHSC, quiescent HSC; MFB, myofibroblast; MMP, matrix metalloproteinases; ECM, extracellular matrix; LPO, lipid peroxidation; ROS, reactive oxygen species; NO, nitric oxide; NOS, nitric oxide synthase; SOD, superoxide dismutase; CAT, catalase; GSH, reduced glutathione; GPx, glutathione peroxidase; ARG, arginase; MTHFR, methylenetetrahydro folate reductase; TNF-α tumour necrosis factor-α; NF-κB, nuclear factor kappa B; IL, interleukin; ΔΨm, mitochondrial membrane potential; M, mitochondria; N, nucleus; Nr2f2, nuclear factor erythroid 2-related factor 2; HO-1, hemoxygenase-1; NQO1, NAD(P)H dehydrogenase (quinone) 1; ARE, antioxidant response element; ABCA1, adenosine triphosphate (ATP)-binding cassette transporter A1, AST, aspartate transaminases; ALT, alanine transaminases; BIL, bilirubin. Adopted from [42].

3. PULMONARY TOXICITY

3.1 Molecular Pathways Underlying Pulmonary Toxicity Related to MTX Administration

It was documented that approximately 25% of RA patients undergoing MTX therapy displayed a range of symptoms including wheezing, coughing, exertional dyspnoea, and other pulmonary indications [54]. Side effects could occur in patients from as early as four weeks following the commencement of the treatment. They are considered an idiosyncratic immune response rather than a dose-related toxic occurrence impacting the lung [55]. Additionally, RA patients who had undergone MTX treatment presented a greater risk of developing lung diseases than other DMARDs [56]. Damage to the lungs associated with MTX could additionally manifest as fibrosis, interstitial pneumonitis or widespread alveolar injury [54]. Therefore, it is critical that recognition is rapid before interstitial pneumonitis worsens to severe pulmonary fibrosis. The pathological mechanism could be separated into the following three categories: (i) inflammatory; (ii) infections; (iii) lymphoproliferative [57]. However, the precise mechanism is complex and the full picture lacks clarity.

Elevated levels of IL-8 in BAL fluid and the build-up neutrophils cause MTX-induced pneumonitis [58]. IL-8 is a primary neutrophil chemotactic element that results in a neutrophilic influx in the lung [59, 60]. The mRNA expression of IL-8 and
the secretion of IL-8 and other cytokines are increased by MTX. Therefore, IL-8 may be integral in pneumonitis out of MTX-induced lung damage [61]. In airway epithelial (A549) cells, the discharge of cytokines such as IL-8, MCP-1 and G-CSF is provoked by MTX-induced pneumonitis [62]. Moreover, in patients with hypersensitivity pneumonitis and sarcoidosis, the discharged IL-8 levels were elevated in their BAL fluid [62]. Pro-inflammatory cytokines, e.g. IL-1β and TNF-α, stimulate the liberation of IL-8; p38 phosphorylation governs the production of IL-8 [61].

There are three main classes of MAPK, i.e. (i) extracellular signal-regulated kinase (ERK); (ii) c-Jun NH2-terminal kinase (JNK); and (iii) p38 kinase pathways [63]. The latter are stimulated by inflammatory cytokines responsible for initiating asthmatic episodes or autoimmune pathology [64]. A MAPK cascade consists of a MAPK kinase kinase (MAPKKK)–MAPK kinase pathway; this is linked by a variety of methods between receptors and transcription targets, upstream and downstream, respectively [64]. In these MAPK signalling cascades, MAPKK is controlled by the phosphorylation of serine/threonine residues on MAPKK, and this kinase prompts the serial activation of MAPK [65]. Finally, MAPKKK–MAPKK–MAPK pathways phosphorylate diverse substrates including transcription factors. The p38 and JNK pathways in the main MAPK pathways are related to chronic inflammation [64].

It was shown that MTX modulated the p38 MAPK signalling cascade (which is the TAK1–MKK3/MKK6–p38 MAPK–MAPKAPK2–HSP27 module [58]. This signalling pathway caused the discharge of IL-1β and IL-8 [66]. IL-1 causes endogenic TAK1 action [67]. TAK1 (an MAPKKK) is a ubiquitin-reliant kinase of MAPKK that intermingles with the controlling proteins TAB1, TAB2 and TAB3 [68]. The autophosphorylation at Thr-184, Thr-187 and Ser-192 was facilitated by the TAK1/TAB1 complex [65]. TAK1 triggers either MKK4 or MKK3/6, both of which are MAPKK phosphorylate, p38 MAPK members [69]. MAPKAPK2 is activated by the p38 MAPK, which then initiates HSP27's phosphorylation [70]. Moreover, the secretions of IL-1 and IL-8 are elevated by HSP27 [66]. These cytokines respond to TAK1, which is upstream of the p38 MAPK [71]. As presented in Fig. 1, the pulmonary inflammatory reaction is the consequence of recycling the IL-1β–TAK1–MKK3/MKK6–p38 MAPK–MAPKAPK2–HSP27–IL-8 module as illustrated in Fig. 3.

It is contended that pro- and anti-inflammatory cytokines' modulation stimulate the pulmonary inflammatory response (Kim et al.) [66,72,73]. MTX's immunoregulatory contribution facilitates a harmony between pro- and anti-inflammatory cytokines. Previous research has demonstrated that IL-1β and IL-8 expression heightened the impact of MTX, whereas conversely, IL-4, IL-6, IL-12, TNF-α, macrophage inflammatory protein-1α (MIP-1α), and macrophage inflammatory protein-1β (MIP-1β) expression reduced it in a dosage-determined way [66]. Pro-inflammatory cytokines are actors in IL-1β, TNF-α, IFN-γ, IL-2, IL-6, IL-8, IL-12, MIP-1α and MIP-1β, and Regulated on Activation, Normal T Expressed, and Secreted (RANTES). Conversely, anti-inflammatory cytokines, i.e. IL-4, IL-10, TGF-β, TNF-α, IL-1 and IL-8 are believed to be of import in inflammatory lung disease and in idiopathic pulmonary fibrosis [73]. Potentially, MTX could stimulate a pulmonary inflammatory reaction through the discharge of IL-1β and IL-8 but not TNF-α in pro-inflammatory cytokines in bronchial epithelial cells. IL-4 may also be significant in the MTX-triggered pulmonary inflammatory reaction. Conversely, cytokines including TNF-α, IFN-γ, and GM-CSF in T lymphocytes constrain secretion in RA therapy, with MTX acting as an agent of chemotherapy [74]. Hence, this forms a fresh molecular foundation of the therapeutic impacts according to the constraint of molecular targets including p38, and transcription factor HSP27, and impeding the discharge of the IL-1 and IL-8 pro-inflammatory cytokines.

4. NEUROTOXICITY

It has been documented that MTX is associated with notable lethargy in some individuals [75], which may reflect the actions of intracerebral adenosine. It is widely acknowledged that adenosine has neuromodulatory properties, and effects of its build-up in the CNS include headaches, nausea, and drowsiness [76]. Adenosine is implicated in the governance of the awake status and somnolence via its operation on the A1 receptors located in the perifornical lateral hypothalamus. This action may be the underlying mechanism of the drowsiness described by some individuals after taking MTX [75]. In paediatric patients, high-dose MTX has been documented to produced marked somnolence and unconsciousness [76]. Some studies have demonstrated that the non-selective adenosine receptor antagonist,
theophylline, is able to offset the toxic effects of MTX on the CNS in this population [76].

Another potential mechanism underlying the adverse cerebral manifestations of MTX may be raised titres of homocysteine and its breakdown products, e.g. the amino acid neurotransmitters homocysteic acid and cysteine sulphenic acid; the latter can cause excitotoxic neuronal demise [77]. Another potential outcome of neurotoxicity linked to MTX is damage to the biopterin metabolism, resulting in reduced monoamine neurotransmitters synthesis [78]. It is accepted that MTX treatment stimulates the development of subcutaneous nodules, which are a build-up of multinucleated giant cells that originated from mononuclear cells [79]. One study employed an in vitro model of giant cell formation to examine nodulosis caused by MTX [80]. The researchers established that the production of multinucleated giant cells is improved by MTX and also by adenosine A1 receptor occupancy. A particular adenosine A1 receptor antagonist counteracts the impact of MTX. The evolution of multiple nodules associated with MTX may therefore arise via the action of adenosine on the adenosine A1 receptors [79].

4.1 Renal Toxicity

It is well-established that renal impairment can be induced by low-dose MTX administration [81]. However, there is a lack of clarity regarding the mechanism underlying kidney injury caused by MTX. Further reports state that kidney injury is a possible consequence of high dose MTX. Urine with a low pH may give rise to precipitation of MTX, together with its principal breakdown product, 7-OH-MTX. This may be an element responsible for intratubular blockage and kidney impairment [82]. Although this process may arise with higher dose regimens of MTX, it is unusual with ongoing treatment with a low dose. Abnormal kidney function associated with MTX may occur via serum adenosine levels and the consequent triggering of A1 receptors within the kidney substance, thus diminishing kidney perfusion and leading to impaired performance [83]. A murine model which simulated kidney impairment associated with low-dose MTX indicated that long-term MTX delivery led to an accrual of MTX within the kidney tissue, together with notable glomerular and tubular injury as a result of heightened oxidative stress [84]. The method of elimination of MTX is predominantly renal. If this route is compromised, and MTX accumulates within the plasma, this may result in adverse effects from the MTX levels, of which bone marrow suppression is a frequent manifestation [85]. Thus, in the presence of a glomerular filtration rate < 30 mL/min, the prescription of MTX, even at a low dose, is ill-advised [86].

Fig. 3. A side-effect of MTX in MAPK signalling pathway. Adopted from [59]
4.2 Other Toxicities

Other toxicities such as endocrinological toxicity, GI toxicity, cutaneous toxicity, haematological toxicity, fatal malfunction or loss, and malignancy can also occur, but at a significantly lower rate of prevalence. Consequently, it is challenging to establish sufficient evidence that low dose MTX toxicity is the cause. Hence, there is greater scope for research on MTX toxicity. The lack of precise mechanism of MTX-induced organ toxicity is an issue, and offers more scope to focus on studies related to MTX toxicity [16].

4.3 Management of Toxicity

Patterns of MTX-induced toxicity may be determined by the means and dose administered. Patients may experience diverse signs and symptoms, and could potentially need hospitalisation and intensive care monitored by physicians and nurses. Typically, the preferred primary approach is to discontinue the MTX administrations as well as the concomitant drugs and monitoring blood parameters, renal parameters, and liver parameters as the initial toxicity developed. The treatment approach should be determined by the clinical symptoms and signs. Usually, these patients can be treated with the following three standard approaches: (i) maintenance of the level of MTX serum; (ii) maintenance of body hydration; (iii) promotion of MTX excretion [87].

4.4 Leucovorin (Folinic Acid) Rescue Therapy

Folinic acid is a leading antidote to MTX toxicity. The function of the folinic acid is essentially to re-establish the diminished intracellular folate. The level of MTX serum determines the administration of folinic acid. This may necessitate a comparatively higher folinic acid concentration on higher MTX concentration. Folinic acid may be inadequate in exceedingly high MTX concentration (even 10-fold higher), particularly in circumstances of renal injury. The level of MTX serum should be measured every 24 h until it reaches 0.2 μmol/L. In cases of MTX single oral overdose ingestion (<1000 mg or <5 mg/kg in children) with good hydration and normal kidney function, high dose folinic acid administration may not be required. This is determined by the clinical status and MTX serum level. Conversely, in cases of MTX under-dosing (intake daily rather than weekly dose) with the important clinical characteristic of MTX toxicity, 10mg/m2/i.v/orally administered every 6 hours with daily monitoring of blood counts, renal function, and other examinations to determine the presence of toxicity may be required. Many studies have confirmed that a lack of an initial increase in the leucovorin dose has resulted in a number of deaths [88-89].

4.5 Body Hydration Maintenance

In order to decrease MTX toxicity, it is critical to maintain body hydration and establish aimed diuresis, as this will remove excess MTX from the body. The output of urine must be sustained at either 600ml over 6h or 200ml over 2h (maintaining an approximate urine output of 2L/m2/day is essential). It is important to sustain fluid intake at approximately 3L/m2/day until the level of MTX serum reaches 0.2 μmol/L. The key to avert renal toxicity and excess fluid is to meticulously monitor and maintain both fluid input and output [88-93].

4.6 Enhance Excretion of MTX

In a low pH, MTX and its breakdown products, 2,4-diamino-N-(10)-methylpterolic acid and 7-OH-MTX, have low solubility. An increase of urine pH from 6.0 to 7.0 correlated with a solubility increase in MTX and its metabolites from 5 to 8 folds. Moreover, sodium bicarbonate administration of 40-50 mEq per litre of IV fluid could potentially avert the creation and deposition of intratubular MTX crystal and improve MTX renal excretion [88-91].

4.7 Managing Delayed MTX Excretion

Renal clearance glomerular, tubular reabsorption, and secretion is pivotal in MTX excretion. MTX-induced renal toxicity primarily occurred through the formation of crystal/deposition and direct tubular kidney impairment. During renal impairment, recommendations are for delayed MTX renal clearance and serum MTX concentrations exceeding 1 μmol/L, glucarpidase (carboxypeptidase enzyme), which has received USFDA approval. Glucarpidase is an amalgamation of 390 amino acids having 83 kDa and created from Escherichia coli. This functions by quickly metabolizing the plasma MTX into the following two inactive metabolites: (i) Glutamate; (ii) DAMPA. Glucarpidase comes into play when the level of MTX serum is or exceeds 10 μmol/L.
and 100% increase in serum creatinine. Following glucarpidase administration, an MTX serum level of 97% or higher is used for reduction within 15 min, but has minimal to no impact on intracellular MTX concentration, resulting in folic acid being the preferred drug for the treatment of MTX toxicities. Glucarpidase is available in vials containing 100 units/vial. Each vial must be reconstituted with 1 ml sodium chloride (0.9%) and injected within 5 min via IV bolus injection. It is necessary to administer folic acid prior to or after the 2 h of glucarpidase administration so as to avert the drug-drug interaction and to prevent diminishing levels of folate [88- 89].

4.8 Supportive Care

Treating low dose MTX toxicity requires supportive care. This could entail daily doses of folic acid, oral or systemic corticosteroids, G-CSF, IV fluids, empirical antibiotic, antifungal, blood product transfusion, renal impairment correction, hepatic abnormality correction, dialysis, dose reduction or management of potential drug interactions, oral care, oxygen supply, and advising patients on MTX usage. It could be beneficial to better comprehend the therapeutic and toxic mechanisms of MTX action. Such an understanding would facilitate the identification of de novo targets for the treatment of inflammatory and autoimmune disorders, whilst additionally minimising adverse event profiles. This is highly significant for the design of new drugs and the development of more targeted therapies, as this will facilitate the reduction of drug toxicity whilst simultaneously preserving effectiveness [91-92].

5. CONCLUSION

It is concluded that a comprehensive understanding of the molecular mechanisms of methotrexate toxic effects was determined in this study. Study also discussed the management of this toxicity.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/76915