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Management of Methotrexate Toxicity

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Abstract

High dose methotrexate (HDMTX) is an important chemotherapy agent in the treatment of cancers in children. Treatment with HDMTX can cause unwanted side effects and induces many types of toxicity (e.g. renal toxicity, liver toxicity, neurotoxicity, hematologic toxicity, pulmonary toxicity, gastrointestinal toxicity and cutaneomucous toxicity). Adding leucovorin rescue provides the advantage of safe administration. However, HDMTX therapy should be initiated only when plasma methotrexate monitoring is available to determine adequacy of drug removal and the risk of serious toxicity. Monitoring of MTX serum level is an effective tool in managing the toxicity profile and guiding the dose of leucovorin. Sufficient hydration, urine alklinization, monitoring of liver and kidney functions and avoiding drugs interaction can also promote safe administration.

Key words
Methotrexate; Side effects; Toxicity; Prevention; Leucovorin

Introduction

Methotrexate (MTX) is a folate antagonist which has anti-inflammatory, and immunomodulatory properties. It is also used in a wide range of malignancies. Furthermore, MTX is used in the treatment of psoriasis and rheumatoid arthritis.

Methotrexate is the most famous chemotherapeutic agent, specifically in childhood malignancies and acute lymphoblastic leukemia (ALL), as it is a crucial component to ALL treatment protocols [1]. MTX is commonly used in high doses (1–8 g/m²) to overcome cellular resistance of testes and central nervous system with low doses [2].

Methotrexate penetrates the cell by active transport through reduced folate carriers (RFC) then it undergoes polyglutamation catalyzed by folylpolyglutamate synthetase. Once polyglutamated, MTX is retained in cells for prolonged periods of time. MTX and its polyglutamates deplete intracellular reduced folate levels by competitively and reversibly inhibiting of dihydrofolate reductase (DHFR), the enzyme that converts dihydrofolate to tetrahydrofolate which is required for continuous replenishment of cells supply of reduced folate and thymidylate synthase (TYMS), resulting in depletion of purines and thymidylate and prevention of RNA and DNA synthesis causing cell death (Fig 1) [3,5]. Methotrexate is highly active against rapidly dividing cells during the S phase of a cell cycle [6].

Many of the adverse effects of HDMTX are very serious and may threat patient life. The early detection, good monitoring and rescue doses help in preventing the occurrence of toxicity.

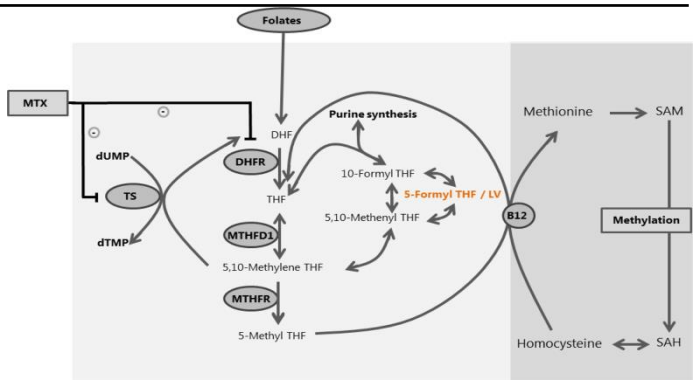

Figure 1: Folate pathway. Leucovorin (5-formyl THF) rescue administration avoids the action of DHFR. SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; DHF: dihydrofolate; THF: tetrahydrofolate; TS: thymidylate synthase; DHFR: dihydrofolate reductase; MTHFD1: methylenetetrahydrofolate dehydrogenase 1; MTHFR: methylenetetrahydrofolate reductase; MTX: methotrexate; LV: Leucovorin [7].

Neurotoxicity

Usually CNS toxicity appears after HDMTX administration or during IT administration. CNS toxicity occurs in nearly about 20% of patients [8]. Manifestations are classified into many grades. Acute manifestations are the most frequent such as nausea, headache, vomiting and meningitis. Acute manifestations are transient and not sever which can appear within two days and disappear after stopping of the infusion. Symptoms of sub-acute MTX neurotoxicity are paraplegia, cerebellar dysfunction and seizure. Sub-acute manifestations occur after MTX initiation by 1-2 weeks. Chronic toxicity is the most critical complication as it is irreversible. Clinically, it can be observed many months to years after MTX treatment when chemotherapy is associated with radiotherapy [9].

The mechanism of CNS toxicity is still not understood, but several theories suggest the interference of MTX with

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transmethylene reaction that is essential in protein and myelin formation, as the reason of toxicity. Some theories suggest the elevation of homocystein is responsible for CNS toxicity [10].

Renal toxicity

The incidence of renal toxicity was reported as 7-8%, but it is very serious. On the other hand the incidence of tubular necrosis is very rare [11].

MTX and its metabolites are insoluble in acidic urine, so increasing the pH of urine results in improving the solubility of MTX and its metabolites. On the other hand, MTX crystals appear in acidic pH causing acute renal failure [12].

There are many risk factors responsible for high prevalence of toxicity such as methotrexate dose, methotrexate duration, low alkalinzation, poor hydration and low rescue dose. Also, drugs that interfere with methotrexate for renal tubular excretion delay the MTX clearance resulting in renal toxicity [13].

Elevation of creatinine clearance level than baseline level is an important indicator of renal toxicity which returns to normal levels within 14-21 days. The cornerstones of renal toxicity management are urine alkalinzation and rescue dose adjustment. Hydration and alkalinzation before, during and after MTX administration are recommended. [14]

Liver toxicity

Acute liver toxicity induced by HDMTX is less common than that induced by low doses [15].

Elevation of liver function was reported in about 25% of patients. Clinically, adjustment of MTX dose was not recommended as this laboratory changes are reversible and transient. The cause of liver toxicity is still unclear [16].

It is advisable to measure liver enzymes and bilirubin levels before MTX administration by 48 hours to be sure there was no indication of liver abnormalities which may be getting worse after the administration [17].

There are many risk factors that increase the prevalence of liver toxicity such as viral infections (virus B and C), cumulative MTX dose, diabetes, drinking alcohol and obesity. Risk factors must be avoided before starting MTX administration [17].

Hematologic toxicity

Hematologic toxicity appears within 1 to 3 weeks and disappears within 3 weeks. Clinically, toxicity appears in the form of thrombocytopenia followed by sever leukopenia; the toxicity may be acute or chronic. Hematologic toxicity induced by low dose is rare with an incidence of 3% [18,19].

The cause of hematologic toxicity induced by HDMTX is still unclear, but several hypotheses suggest delay elimination of methotrexate causing severe neutropenia and thrombocytopenia [20].

There are many risk factors that increase the prevalence of pancytopenia like low albumin level, deficiency of folic acid, co-administration of some drugs with HDMTX administration, infections, dehydration and renal dysfunction [20].

It is advisable to avoid co-administration of drugs especially those which compete with MTX excretion to prevent delayed elimination. Rescue doses and duration must be adjusted [21,22].

GIT toxicity

GIT toxicity occurs with both low and high doses. The incidence of patients who suffer from vomiting and nausea was about 25% even with antiemetic administration; others suffer from abdominal pain or diarrhea. Dexamethasone ampoule is recommended to control vomiting and additional hydration provided to replace the lost fluids [23,24].

Oral mucositis can become a dose-limiting toxicity as the high dose may increase cellular damage of rapidly dividing epithelial cells all over the GIT tract. Low rescue doses may lead to an impairment of epithelial cell growth and regeneration. Ice chips are used to prevent and treat oral mucositis [25,26].

Pulmonary toxicity

Pneumonitis is a very serious side effect of low dose MTX, but rare with high dose MTX. It is reported in 1-2% of patients [27]. MTX can also excite lung fibroblasts and epithelial cells to prompt recruitment of eosinophil [28]. Also it has been reported that neutrophils are involved in the pathogenesis of lung fibrosis [29-30].Symptoms, like nonproductive cough (most common symptom), malaise, fever, and dyspnea may occur from few days after the administration and may be continuous for more than a year after the beginning of MTX therapy and also several weeks after MTX discontinuation [31,33].
The cornerstone of pulmonary toxicity is the usage of corticosteroids with immediate stoppage of MTX administration [34].In more advanced cases, use of cyclophosphamide is necessary [35].
Cutaneomucous toxicity
There are many mucocutaneous reactions that are induced by MTX administration like skin burning sensation, mucosa ulcers and photosensitivity. The most frequent symptoms are urticaria and vasculitis [36].
The mechanism of skin toxicity is still not known, but there are many hypotheses that explain the cause of skin toxicity which is mainly due to hypersensitivity reactions also others suggest that MTX may prompt cutaneous small vessel vasculitis in those who suffer from collagen vascular disease and administer low dose of MTX [37].

Prevention of MTX-HD Toxicity

To avoid HDMTX toxicities there are some general strategies of pre, during and post HDMTX administration that are recommended to patients treated by HDMTX regimens

Determination of kidney function

MTX is eliminated by the kidney. Clinically, measurements of kidney function (creatinine clearance, urea and urine output) before, during and after HDMTX administration must be carried out. Urea normal range is 15-45 mg/dL and normal creatinine clearance level is 90-120 ml/min [38]. A lower level of creatinine clearance (below 15ml/min.) before administration is a predictor of kidney toxicity occurrence [39-40].

Furthermore, elevation of creatinine laboratory level, normal range is 0, 5-1, 2 mg/dL, [38] is an indicator of delayed MTX clearance and kidney dysfunction [41].
Dose reduction is necessary for patient suffering from low creatinine clearance level. For example, reduction of 75% of MTX dose is recommended when Cr Cl level is 10-30 ml/min and the dose should be reduced to 50% when Cr Cl level is 30-60 ml/min [12].

Urine Alkalization

Alkalization of urine by fluids with 40 mEq/L sodium bicarbonate has a great role in minimizing intra tubular crystal formation. Practically, urine pH must be checked and HDMTX should be administered only when the urine pH is ≥ 7.0 and level maintained till MTX plasma levels become fewer than 0.1 micromole. Acidic urine pH increases the probability of nephrotoxicity so sodium bicarbonate dose can be repeated to achieve alkaline pH [42].

Promoting adequate hydration

As previously mentioned, methotrexate and its metabolites are mainly cleared by the kidney. Aggressive hydration is needed to promote high flow rate and to prevent precipitation [13].
Hydration with 150-200 mL/ m^2 per hour is recommended before HDMTX administration by 48 hours and it should continue for two days after the administration [12].

Avoiding drug interactions

Avoiding co-administration of drugs that increase the HDMTX toxicity is necessary. Toxicities of HDMTX may occur if the drug has the ability to displace MTX from serum protein like salicylates, phenylbutazone, phenytoin and sulphonamide as 50% of MTX is bound to serum protein [43]. Non-steroidal anti-inflammatory drugs have the ability to inhibit renal clearance of MTX and displace protein-bound MTX, and consequently elevating creatinine level and prolonging MTX serum concentrations [44]. Co-administration of probenecid with HDMTX prevents renal tubular transport. Also, gentamicin and cisplatin (high nephrotoxic drugs) prevent tubular transport and increase the incidence of toxicity [45].

Third space fluids drainage

Drainage of third space fluids, pleural effusion or ascites before initiation of HDMTX is recommended to prevent toxicity as third space fluids cause prolongation of MTX half-life and its concentration. Thus accumulated drug will sustain back-diffusion into the intravascular compartment [46].

Monitoring of MTX plasma concentration

The most important part of HDMTX therapy is monitoring of MTX plasma level to identify patients who are at high risk of MTX toxicity [47]. Variability in plasma concentration from patient to patient were observed after administration and within a patient on followed cycles although the dose and the duration of MTX were fixed so close monitoring of MTX level is important to identify any change in creatinine clearance [47]. The normal serum level of MTX at 24 hrs of MTX administration should be above 1µmole and below 1µmole at 48 hrs of MTX administration [48].

MTX plasma level is a good indicator of toxicity especially renal toxicity. Monitoring must be carried out in the same time of hydration and alklinization adjustments. Also recue doses are adjusted to be suitable with the leucovorin monogram timeframe (fig 2) [49].To obtain safe administration of HDMTX in hospitals when MTX monitoring is not available, daily monitoring of Cr Cl, urine output, pH of urine, liver function and twice daily examination of mucosal membranes must be carried out, as reported in Recife, Brazil [50].
Management of HDMTX Related Toxicity
Leucovorin
Administration of HDMTX can be fatal if not followed by folic acid rescue therapy administration (Leucovorin, LCV). Earlier studies showed that LCV could save both normal cells and tumor cells from the adverse effects caused by methotrexate. This phenomenon was named as folate over-rescue principle [51].
Leucovorin (5-formyl-tetrahydrofolic acid) was firstly famous as "citrovorum factor" in 1984 when scientists discovered it. FDA approved LCV in 2002. Nearly half of the administered dose is in the active form as leucovorin consists of multi stereoisomers which are mostly inactive [52].
Mechanism of action
Leucovorin and methotrexate are structural analogues to folic acid so both of them compete for the same cell transport processes, polyglutamylation, binding to enzymes (DHFR and TS) and albumin binding. Leucovorin is folic acid in its active form (reduced form) which could bypass DHFR enzyme by repairing purine and pyrimidine synthesis so DNA and RNA synthesis are continued in the presence of MTX. LCV is mainly effective in the management of gastrointestinal toxicity, CNS toxicity and myelosupperetion induced by HDMTX [53].

Administration and pharmacokinetics

LCV can be taken in more than one dosage form. It can be taken orally which is not preferable because of vomiting and the slow onset of action (15minutes). Leucovorin can be taken intramuscularly with the onset of action (25 minutes). Also it can be taken intravenously which is preferable with vomiting or poor absorption and its onset of action appears within 5 minutes. When used as a part of chemotherapeutic regimens, intravenous dosing is preferred. It is important to note that leucovorin cannot to be taken intrathecally as it would be lethal. Leucovorin is mainly eliminated by the kidneys in the form of 10-formyl tetrahydrofolate and 5, 10-metheny tetrahydrofolate [54].

After 42 hours from MTX administration, 10-15 *mg*/ m^2 should be administered every 6 hours until MTX serum concentration drops below 10^{-8} moles. Therapeutic effects of MTX may be affected by co-administration of MTX and leucovorin. On the other hand, if leucovorin therapy gets delayed beyond 42 hours, tissue toxicity may be permanent [54].

Monitoring of leucovorin

Monitoring of serum MTX once every 24 hours until the level falls below the threshold and renal function must be done with daily check of the serum creatinine levels, Fig 2. If the serum creatinine rises by more than 50% over the previous days baseline or if the measured methotrexate one day after admission level is greater than 5 x 10^{-6} moles or serum methotrexate value at two days is greater than 9 x 10^{-7} moles, rescue dose should be increased to 100 mg/m^2 taken IV till the serum methotrexate value falls below 10^{-8} moles. Hydration

and alkalinization of urine are necessary. Leucovorin must continue till the methotrexate level falls below 0.05 micro molar. If delayed excretion is suspected or if raised creatinine levels appear, the rescue dose must be increased [53-54].

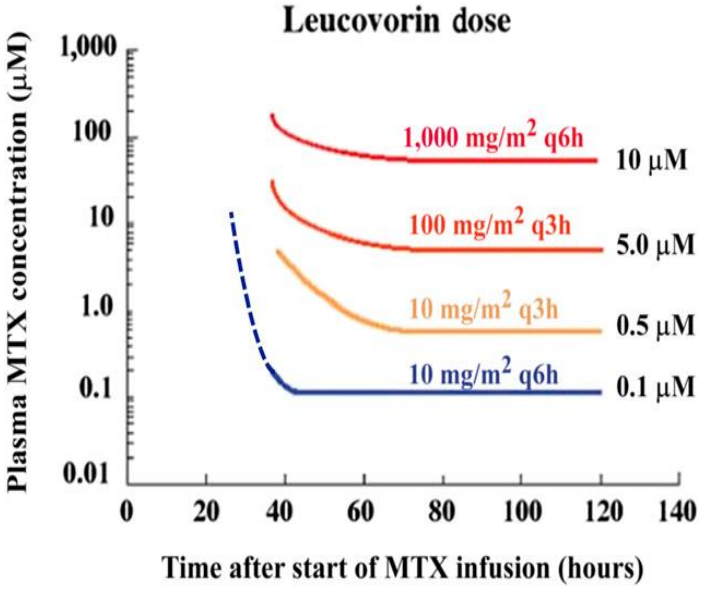

Figure 2: Pharmacokinetically guided leucovorin rescue based on plasma MTX levels after high-dose MTX.leucovorin is administered after 42 hours after HDMTX infusion where leucovorin dosing must be increased dramatically when MTX plasma levels are elevated above 5micromole as leucovorin compete with MTX to enter cells via the reduced folate carrier. Adjustment of leucovorin dose is based on the MTX plasma level at each time point after the start of the MTX infusion. For example, if at hour 60 the MTX concentration is 100 micromoles it falls above the red line and the recommended leucovorin dose would be 1,000 mg/ m^2 every 6 hours. If at 100 hours the methotrexate concentration decreases to 3 micromoles (above the yellow line, below the orange line), then the recommended leucovorin dose would decrease to 10 mg/m^2 every 3 hours. The dotted lines indicate extrapolated values based on modeling and clinical trial experience following the original publication (Obtained after permission, 55).
Abbreviation: MTX, methotrexate

Conclusion

Monitoring of MTX serum concentration with adjustment of dose and rescue promote safe administration of HDMTX in pediatric protocols.

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