ORIGINAL RESEARCH PAPER

General Medicine

METHOTREXATE TOXICITY: CLINICAL FEATURES, MANIFESTATION, MANAGEMENT AND COMPARISON BETWEEN TREATMENT MODALITIES.

KEY WORDS: Methotrexate (MTX), Toxicity, Leucovorin, Folinic acid, Filgratin.

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ABSTRACT

Methotrexate is a potential chemotherapeutic drug. It is used in the treatment of a variety of illnesses including cancer, rheumatoid arthritis, systemic lupus erythematous, and psoriasis. Methotrexate toxicity is one of the common toxicity noticed in routine practice. The most common cause of acute methotrexate toxity is an accidental overdose of the tablets by patients. Here we describe three cases,

FIRST CASE: A 65 year old patient diagnosed as arthritis on methotrexate therapy since 6 months, self medicated as qd for one week, she was treated with Inj Leucovorin (folinic acid);

SECOND CASE: A 50 yr old female diagnosed with discoid lupus erythematous on Methotrexate therapy, administered tab. Methotrexate qd for 5-6 days, she was treated with Inj Filgrastim;

THIRD CASE: A 80 year old male patient diagnosed as arthritis on methotrexate therapy 2.5 mg 4 times a week, but due to prescription error patient had 10 mg tablets 4 times a week for two weeks. He was treated with oral Folinic acid 5 mg qd for 3 days and afterwards was treated with Inj Filgrastim for 4 days. **Conclusion:** Both Leucovorin and Filgrastim showed effective mode of treatment for Methotrexate toxicity. But Leucovorin is better among both due to its good safety profile, lesser side effects, is cheaper, and is pharmacological antagonist of methotexate. So Leucovorin should be admistered as primary treatment of choice for Methotrexate toxicity.

INTRODUCTION:

Methotrexate is a potential metabolic anti cancer drug1, in proper doses it remains effective therapy for cancer, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. Methotrexate toxicity is one of the common toxicity noticed in routine practice. Methotrexate toxicity develops due to increased patient susceptibility during treatment, excessive parenteral or intrathecal administration, and therapeutic errors by patients (e.g. taking MTX orally daily instead of weekly). Well known signs of methotrexate toxicity include oral ulcer, gi ulcers,2 bone marrow suppression, pancytopenia, gastrointestinal (GI) mucositis, hepatotoxicity, pulmonary toxicity, and acute renal failure.3 Here we present three cases of Methotrexate toxicity treated with different modalities with different clinical outcome.

CASE 1: A 65 year old female patient came with complains of difficulty in swallowing, difficulty in opening mouth, multiple oral ulcers, with history of fever and chills since 7 days. She was diagnosed as rheumatoid arthritis 6 months and was on Tab Methotrexate 10 mg weekly, but due to excruciating pain she self medicated with tab Methotrexate qd for consecutive 4-5days before admission.

On physical examination the patient was conscious oriented with pulse-80 b/min, BP -130/80 mmHg, SPO2-97% off O_2, respiratory rate of 20 cycles per min febrile with temperature of 101Patient had multiple erythematous erosions on lips, oral ulcers. Systemic examination was unremarkable. Laboratory reports revealed Hb-9.3gm/dl, TLC-700 cubicmm3, platelet count 45000, sr. Creatinine- 2.7mg/dl, sr. Urea-115mg/dl, LFT'S, prothrombin time, peripheral smears, sr. Iron, total iron binding capacity, urine, stool analysis, chest X-ray, USG A/P, ECG were within normal limits. Patient was even checked for infection like dengue, leptospira, malaria, but all were negative.

Based on clinical and lab findings a diagnosis of Methotrexate poisoning was made. The patient was started on Inj Leucoverin (folinic acid) 15 mg intravenousaly for every 6 hours. She was also supported with systemic antiobiotics, oral folic acid and oral antifungal therapy. After 7 days of therapy, patient was symptomatically better with total leucocyte count of 8700 and platlet count to 4.80 lakhs.

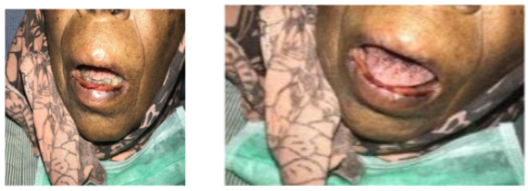
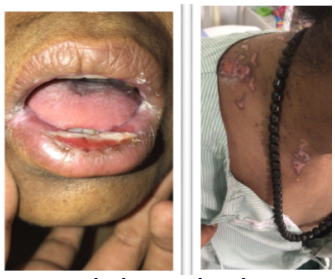


Figure1,2 suggest oral ulcer cause by MTX toxicity

CASE 2: A 50 year old female, a case which presented as multiple oral ulcer since 8 days. Patient also complained of hair loss, multiple joint pain and history of difficulty in swallowing. Patient was treated in outside hospital as vitligo (? Discoid lupus erythematous) and was prescribed on Tab Methotrexate 10 mg once weekly. On physical examination patient was conscious and oriented with pulse 82 b/min, BP- 120/84 mmHg, SPO2- 97% off O2, respiratory rate of 16 cycles per min, and was afebrile. Patient had multiple hypopigmented erythematous plaques on face, upper limb and on neck. Systemic examination was unremarkable. Laboratory reports revealed HB- 9.9 gm/dl total leucocyte count 2800 cubicmm^3, platlet count- 43000/cumm, ESR 45/µ, MCV-87fL, sr. Creatinine- 0.8 mg/dl, blood urea- 38 mg/dl, other parameter like LFT'S, prothrombin time, peripheral smears, sr. Iron, total iron binding capacity, urine, stool analysis, chest X-ray, USG A/P, ECG were within normal limits. Patient was even checked for infection like dengue, leptospira, malaria, but all were negative. Culture was sterile after incubation. Patient was continued on Tab Methotrexate 10 mg qd daily. On clinical scenario she was labelled as DLE. After 4 days patient symptoms worsen and laboratory reports showed remarkable leucopenia with total count of 800 cubic mm3 HB- 8.9 Platelet count of 1.50 lakh/cumm. ANA (Anti Nuclear Antibody) were positive.

Based on clinical and labarotary findings it was suggestive of Methotrexate poisoning. Patient was started with Inj Filgrastim 5µg/kg/day subcutaneous once a day dose, systemic antibiotics, oral antifungals, anti-histaminic, topical steroids, were started. After 5 days of therapy patients symptoms were recovered with total leucocyte count of 5800cubicmm3, platelet count 2.25 lakh/cumm.



FIFURE 3,4 suggest oral ulcer and erthymatous rash over neck

Case 3: A 80 yr old male patient, presented as multiple oral ulcers, multiple joint pain, difficulty of swallowing, burning sensation over tounge while having solids or liquids since 5-6 days. Patient is known case of rheumatoid arthritis and was on Tab. Methotrexate 2.5 mg qd four times a week, but due to prescription error patient received Tab Methotrexate 10 mg qd dose four times a week for 15 days. On physical examination patient was conscious oriented with pulse rate of 70 beats/min, BP of 110/70mmHg, SPO_2-98%off on room air, respiratory rate of 14 cycles /min and febrile. Patient had multiple hypo-pigmented erythematous patches over neck, chest, back. Systemic examination was unremarkable. Laboratory findings revels HB-7.6 gm/dl, total leucocyte count of 300 cubicmm^3 , platelet count -30000 per cubicmm^3 ESR-50 mmHg serum creatinine levels of 1.2mg/dl, blood urea 54mg/dl, other parameters like Liver function test, Prothrombin time, peripheral smear, urine routine were within normal limit. Patient was checked for Dengue, Malaria, Chickenguniya, Leptospira and were negative. Culture was sterile after five days of incubation. Based on clinical and lab findings it was suggestive of Methotrexate toxicity, patient was started with Tab. Folinic acid 5mg once a daily for first 3 days but due to poor response to oral therapy, patient was started on Inj. Filgrastim 5µg/Kg/day S.C. once a day for 4 days. Systemic antibiotics, oral anti-fungal, anti-histaminic, topical steroids were given as adjuvant. Patient's symptoms recovered with total leucocytes count of 4700 cubicmm^{3}and platelet count of 1.50 lakh/mm^3.

DISCUSSION:

Methotrexate is one of the effective drugs but is one of the potential toxic drugs, it is been in use since 1960s and have generated impressive round of safety with careful monitoring[4]. Mylosupression and gastrointestinal mucositis are primary toxic effect of methotrexate.[1] The mucosal cells are more sensitive to Methotrexate than precursor in the bone marrow because of greater accumulation and persistence of Methotrexate in the intestinal epithelium. Methotrexate inhibits mitosis of the cells by antagonizing folic acid required for deoxyribonucleic acid (DNA) synthesis of cells. Once in the cell, Methotrexate inhibits dihydrofolate (DHF) reductase, an enzyme responsible for the conversion of DHF to tetrahydrofolate (THF). Consequently, there is reduction in thymidylate and purine biosynthesis. DNA synthesis eventually halts and cells can no longer divide. Hence cells with the capability of effective polyglutamination such as leukemic myeloblasts, synovial macrophages, lymphoblasts and epithelia are more susceptible to the action of methotrexate.[5]

Several factors have been identified which can precipitate Methotrexate toxicity. The most common risk factors are an alteration in Methotrexate dosage and the use of non-steroidal anti-inflammatory drugs.[3] Other possible contributing factors are renal insufficiency (because Methotrexate is excreted unchanged primarily by the kidneys), infection, pustular flare of psoriasis and older age (55 years or more).[2] Drugs can increase the risk of Methotrexate toxicity either by decreasing renal elimination of Methotrexate (aminoglycosides, cyclosporine, non-steroidal anti-inflammatory agents[2], sulfonamides, probenecid, salicylates, penicillins, colchicines, cisplatin and other renotoxic drugs), or by displacing Methotrexate from protein binding sites in the plasma (salicylates, probenecid, sulfonamides, barbiturates, tetracyclines.[4] Synergistic toxicity occur when Methotrexate is used with trimethoprim-sulfamethoxazole, ethanol and pyrimethamine.

The risk of toxicity secondary to Methotrexate is even greater if additional Methotrexate is administered sooner than the usual scheduled weekly dose, because a new population of dividing cells in the S phase will be targeted.[6] Rapidly proliferating cells have a greater susceptibility to methotrexate because more cells are in the S phase, where methotrexate exerts its effect.[7]

Infection may be risk factor for bone marrow toxicity because the bone marrow is producing more neutrophils thereby increasing the number of susceptible cells.[8]

Folinic acid is the antidote of choice for treating MTX toxicity. This rescue regimen replenishes intracellular stores of reduced folate and attenuates the MTX toxicity. Ideally, the serum levels of MTX should be estimated in all cases of acute MTX toxicity, however; the facility for serum MTX measurement is not widely available, and most cases are managed on clinical grounds.

TABLE 1: Chronology of events in MTX toxicity

Acute toxicity	Number of days after MTX use
Mucositis	3-5
Maculopapular rash	1-5
Hepatitis	1-10
Myelosuppression	7-10
Renal toxicity	1-3
Ocular irritation	1-3

MTX: Methotrexate

A vast majority of Methotrexate is cleared by kidney (more than 90%). A satisfactory diuresis must be estabalished and fluid input should be approximately 3L/M² and aim for urine output of approximately of 2L/M² until level of Methotrexate falls <0.2 µmol/L. Methotrexate and its metabolite (2-4Diamino-N10), Methylpteroic acid (DAMPA) are poorly soluble at acidic pH levels. An increase in urine pH from 6 to 7. Increases the solubility of Methotrexate and its metabolite by 5 to 8 folds an prevents crystal Deposition. Leucoverin "rescue" therapy treatment refers to therapy used for patients rescue. Intentional high Dose Methotrexate dossing ranges from 10-25 mg/m² IV or IM 6 mg to 72 hours.[10] The dosage for prevention with renal compromise is 150 ml/m/3hrs. Both form of Leucovorin therapy are dependent on renal clearance. Adverse effects from Leucovorin therapy are not common, allergic or anaphylactic reaction has been reported but not commonly. Regular neurological checks are adviced. Recombinant Granulocyte Colony Stimulating factors (G-CSF) therapy reduces severity of neutropenia and recurrent risk of neutropenia. Recombinant human G-CSF acts on haematopoietic cells to Stimulate production, maturation and activation of neutrophills.[9]

In our study, all of the cases were diagnosed with methotrexate toxicity. First patient was given Inj. Leucoverin, second patient was treated with Inj. Filgrastim (G-CSF), third patient was treated with Tab Folinic acid 5 mg for first 3 days and afterwards patient was given Inj. Filgrastim for 4 days. Patient who was treated with inj. leucovorin showed earlier rise of total leucocyte count. Patient had final count of 8700 cumm^3. Patient who was treated with only Inj Filgrastim showed steady rise of count of patient 5800 cumm^3 significantly low as compared to inj. Leucoverin. The patient treated with oral Folinic acid for initial 3 days and afterwards

Lab Investigation	Case 1			Case 2			Case 3		
	On Admission	After4days	On Discharge	OnAdmission	After 4days	On Discharge	On Admission	After 3days	On discharge
Hb	9.3	7.4	10.1	9.1	9.1	9.6	7.6	8.0	9.5
TLC	700	4300	8700	800	1900	5800	300	700	4700
PLATLET COUNT	45000	90000	4.80 LAKHS	1.50 LAKHS	2.10 LAKHS	2.25LAKHS	30000	30000	1.50 LAKHS

supplemented with Inj Filgrastim showed very much less rise of total leucocyte count initially to oral folinic acid therapy and even after starting Filgrastim patients final count was significantly lesser compared to either therapy of Inj Leucoverin or of Inj Filgrastim.

Patient treated with Leucovorin had less side effects and early recovery as compared to Filgrastim. Maculopapular rash, oral ulcers healing was also accelerated in Leucovorin compared to Filgrastim. Filgrastim have side effect such as aching or pain in bones and muscles, diarrhoea, constipation, hair loss, headache, tired feeling, skin rash , nosebleeds, bloody urine, vomiting ,fever and local tenderness at injection site which were not seen our cases (are common in therapy).

CONCLUSION:

Both Leucovorin and Filgrastim are effective mode of treatment for Methotrexate toxicity. Both can be used as effective modility of treatment with relative very good safety profile. But Leucovorin is better among both as it have good safety profile, lesser side effects, is cheaper, it's pharmacological antagonistic activity for methotexate and it also decreases severity of other conditions associated with Methotrexate such as oral ulcers and rash . So Leucoverin should be used as primary treatment of choice for Methotrexate toxicity and Filgrastim should be treated as reservoir and used in refractory cases.

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