

METHOTREXATE INDUCED ORAL MUCOSITIS AND BONE MARROW SUPPRESSION IN PSORIATIC PATIENT

ABSTRACT

Methotrexate is an antimetabolite which binds to dihydrofolate reductase enzyme and used in the treatment of malignant disorders and autoimmune diseases. Myelosuppression is a serious complication of methotrexate toxicity. The following case describes a case of 67 year old male patient diagnosed with psoriasis and wrongly taken methotrexate 7.5 mg on daily basis for 3 days and twice daily for 4 days. He presented with oral mucositis and his lab reports showed myelosuppression. Our case emphasizes the significance of effective patient counselling to ensure the understanding of prescription and to prevent drug toxicity.

INTRODUCTION

From 1950s, Methotrexate (MTX) is a widely used systemic immunosuppressive agent and by 1951, MTX was introduced as antipsoriatic agent, it is approved by FDA for this indication in 1972. MTX is a folate antimetabolite which binds to dihydrofolate reductase enzyme which leads to impaired DNA synthesis and repair^(1,2). Apart from the use of MTX in malignant disorders, it is also taken orally in low doses to control the conditions like rheumatoid arthritis and psoriasis³. MTX is considered as a drug that is relatively safe when it is prescribed at low dose regimen that is not exceeding 25mg/weekly. The severe acute toxicity is rare and mostly presents with cutaneous ulceration, bone marrow suppression and mucositis^{4,10,11}. Approximately 78% of MTX treated psoriasis patient develop adverse drug reactions (ADR) where nausea and vomiting are common adverse reaction with ecchymosis, reversible alopecia, pruritus and in severe cases include acute ulcerations of psoriatic plaques, toxic epidermal necrolysis and mucosal erosions⁵. Most cases occurs as a result of the inadvertent overdosing due to erroneously taking drug daily⁴.

CASE REPORT

A 67 year old, male patient with known case of Diabetes mellitus and psoriasis was admitted to the hospital with complaints of psoriasis vulgaris. He was newly prescribed MTX, with advice to take MTX 7.5mg tablet once weekly, but the patient had wrongly taken once daily for 4 days and then 7.5mg BD for 3 days. Cumulative dose was 75 mg MTX. He developed oral mucositis and psoriasis vulgaris over lower limb, elbow and leg. His laboratory investigations revealed myelosuppression with Hb:10.2 g/dl, WBC:3540/ mm³, RBC:3.5 million/mm³, platelets:71,000/mcL, also the creatinine was 1.5 mg/dL, urea:65 mg/dl and sodium 133 mmol/L. Based on physical and laboratory findings and temporal association, MTX toxicity was diagnosed. The patient was admitted in the hospital and treated with IV fluids NS,RL, Inj. Folinic acid, Inj. Vitamin B complex, T.Pantoprazole, Ointment Clobetasol, T.Folic acid and Antibiotics were given.

DISCUSSION

In dermatology, MTX has used as a relatively safe drug dosage(7.5mg to 25mg/week), with the toxicity and side effects associated with dose dependent mechanisms or idiosyncratic. The latter occurs mostly in cells that proliferate faster, like hematopoietic bone marrow cells, and epidermal cells². A low dose MTX in psoriasis infrequently produces toxicity, and most of those occur due to the failure to adhere to the recommended guidelines. The risk of the toxicity is more if additional doses of methotrexate administered than the usual scheduled weekly dose⁶. In our case, the patient took 7.5mg once daily for 4 days and then 7.5mg BD for 3 days following he developed oral mucositis and psoriasis vulgaris. The patient has been recovered on treatment with IV fluids, injection folinic acid and other supportive treatment within 6-8 days. Methotrexate toxicity has its impact on skin, gastrointestinal mucosa, bone marrow, liver and kidneys. Skin ulceration due to MTX toxicity are restricted to psoriatic plaques by higher uptake of MTX by hyperproliferative psoriatic plaques than the normal skin.⁶.

In renal impairment cases, low doses are enough to cause bone marrow suppression and also diabetes mellitus may have role for altering the pharmacokinetics of MTX by physiological environment altering of the body⁷. In the year 1996, a literature review by Pearce and Wilson have identified 47 cases of MTX induced skin ulceration which was reported between the years of 1951 and 1967 and further of 17 cases between the year 1967 and 1996 (including two of their own patients and those of which by Roenigk et al. and Lawrence and Dhal)⁸.

The treatment is done with the immediate suspension of the drug and administration of parenteral folinic acid in the dose of 10mg/m² of body surface. Folinic acid is an antidote of choice used for the MTX toxicity. It is said that earlier the treatment of folinic acid, higher the success rate, mainly concerning the venture to avoid or to interrupt myelosuppressive effects². In most cases bone marrow toxicity is dose dependent and responded to folinic acid. Pancytopenia, leukopenia, anemia and thrombocytopenia are rarely occur. In a review by Gutierrez-Urea and associates the clinically significant pancytopenia was found in 1% to 2% of rheumatoid arthritis on MTX therapy⁹.

Management of delayed Methotrexate excretion : Glucarpidase (carboxy-peptidase, CPDG2) which was approved by US FDA for treatment of the increased plasma MTX concentration (>1µmol/l) in patients with delayed MTX clearance due to the impaired kidney function that may result in bone marrow suppression⁶.

Methotrexate is the best option with great therapeutic value for psoriasis and most importantly it should be well guided by the physician².

CONCLUSION

Our case presented with complaints of psoriasis vulgaris, oral mucositis with MTX induced bone marrow suppression shows that the improper dosage of methotrexate will lead to toxicity as it has low therapeutic index. Therefore it is important to ensure the correct understanding of prescription. Dispensing of the MTX drug in weekly dosage pack communicating effectively with the patients about unusual administration of dosage regimen can reduce adverse effects. Physicians should embolden the feedback of patients to ensure that patient understands the weekly dosage regimen schedule and this medication should not used "as needed" for symptomatic control. MTX is well established element of the dermatology therapeutic arsenal governed by robust guidelines for introduction and monitoring which aims to minimize the patient risk ^(6,8).

REFERENCE

1. Bidaki R, Kian M, Owliaey H, Zarch MB, Feysal M. Accidental chronic poisoning with methotrexate; report of two cases. Emergency. 2017;5(1).

2. Souza CF, Suarez OM, Silva TF, Gorenstein AC, Quintella LP, Avelleira JC. Ulcerations due to methotrexate toxicity in a psoriasis patient. *Anais brasileiros de dermatologia*. 2016 May;91:375-7.
3. Sosin M, Handa S. Low dose methotrexate and bone marrow suppression. *Bmj*. 2003 Feb 1;326(7383):266-7.
4. Yélamos O, Català A, Vilarrasa E, Roé E, Puig L. Acute severe methotrexate toxicity in patients with psoriasis: a case series and discussion. *Dermatology*. 2014;229(4):306-9.
5. Srinivasa BM, Padmini SN, Kumar P, Philip AA, Presannan AK, Thomas R, Arif A. A Case Report on Methotrexate Overdose Induced Pancytopenia and Mucocutaneous Ulcerations. *Indian Journal of Pharmacy Practice*. 2020;13(4).
6. Karunakar P, Garimella VR, Yerram C, Gogula A. Acute methotrexate toxicity in psoriasis. *International Journal of Research*. 2019 Jul;5(3):652.
7. Manappallil RG, Prasan D, Peringat J, Biju IK. Severe bone marrow suppression due to methotrexate toxicity following aceclofenac-induced acute kidney injury. *Case Reports*. 2018 Jun 5;2018:bcr-2018.
8. Manappallil RG, Prasan D, Peringat J, Biju IK. Severe bone marrow suppression due to methotrexate toxicity following aceclofenac-induced acute kidney injury. *Case Reports*. 2018 Jun 5;2018:bcr-2018.
9. Gonzalez-Ibarra F, Eivaz-Mohammadi S, Surapaneni S, Alsaadi H, Syed AK, Badin S, Marian V, Elamir M. Methotrexate induced pancytopenia. *Case Reports in Rheumatology*. 2014 May 27;2014.
10. Noorsaeed, A. S., Aljohani, M. S., BinAfif, K. S. A., Alsaywed, R. A., Bakhshwain, M. A., Alharbi, R. M., Bukhari, H. A. M., Albalushi, O. M., Aljuhani, A. A., Batarfi, A. A., Subahi, A. F., Alghamdi, A. M. S., khallaf, M. tariq and Asiri, Z. A. (2021) "Management of Chemotherapy Induced Mucositis", *Journal of Pharmaceutical Research International*, 33(59B), pp. 220–226. doi: 10.9734/jpri/2021/v33i59B34372.
11. Martins LJ, Borges AF, Ferreira GZ, Sansavino SZ, Siosaki AT, Tabata A, Santos PS. Material selection for constructing an intraoral stent used in radiotherapy: analysis of density and structure. *Br J Med Med Res*. 2016;16(9):1-6.