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LOW-DOSE METHOTREXATE-INDUCED PANCYTOPENIA: QUICKLY REVERSIBLE WHEN SPOTTED EARLY

Medicine

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ABSTRACT

An older adult patient with compromised glomerular filtration rate was treated with methotrexate 12.5 mg/week for an inflammatory joint disease, accompanied with daily folic acid. After 20 months he developed lassitude and pancytopenia was discovered (predominantly anaemia) suspected as being methotrexate-induced (Naranjo probability score 8). Methotrexate was immediately discontinued and leucovorin (folinic acid) administered with rapid recovery of the myelosuppression. The basis, implications, risk factors, and prevention of this potentially dangerous side effect of methotrexate are discussed.

KEYWORDS

INTRODUCTION

Methotrexate, besides its role as an antineoplastic agent, is being widely used in rheumatology, especially for the treatment of rheumatoid arthritis (RA), but also for other inflammatory conditions.

Methotrexate (MTX) is the most commonly used disease-modifying anti-rheumatic drug (DMARD) and considered as the anchor drug among DMARDs, exerting immunomodulatory, anti-inflammatory, as well as atheroprotective effects (1).

In early rheumatoid arthritis management, MTX treatment is often the first choice, and its use has been associated with improved signs and symptoms, achievement of remission in disease activity, delay in radiographic progression, and prolonged life span attributed to decreased cardiovascular mortality.

However, MTX use may be associated with myriad adverse effects (ADR), the most common being gastrointestinal toxicity (e.g. stomatitis) and central nervous system toxicity (e.g. headache, fatigue). Some toxicities are far more harmful, especially in the elderly (>65 years old), where an interplay of pharmacokinetic factors (absorption, distribution, metabolism, and elimination of drugs), pharmacodynamics, and external factors (predominantly polypharmacy and potential drug interactions) increase risk of side effects (2, 3).

We report an older adult patient who received MTX uneventfully for a long time before developing symptomatic pancytopenia, to increase awareness of an uncommon side effect and its relation with age, glomerular filtration rate (GFR), and cumulative dose of MTX.

Case Report

A 78-year-old man developed symmetric polyarthritis involving large and small joints without morning-stiffness or extra-articular involvement. Anti-CCP were >300 EU/ml with ANA (homogenous, 1:160), and ESR 98 mm/hr. Rheumatoid arthritis was diagnosed after an underlying disease (e.g. malignancy) was ruled out. Methotrexate (MTX) 12.5 mg/wk with daily folic acid, hydroxychloroquine 400 mg/day, and prednisone 5 mg/day were started. Full clinical and laboratory remission was obtained within 8 weeks, and maintained with tapering prednisone to 1 mg and stopping hydroxychloroquine. Autoantibodies persisted.

The patient had obesity, diabetes, and hypertension well-controlled on losartan, amlodipine, vildagliptin/metformin and rosuvastatin. Creatinine was 1.4 mg/dL, proteinuria 380 mg/d, and Hb 11.3 g/dL.

After 20 months marked lassitude developed. Hb was 8.6 g/dL (MCV 94), WBC $3.8x10^9$/L (neutrophils $2.4x10^9$/L), and platelets $137x10^9$/L. GFR was unchanged. MTX level was 0.39 micromole/L (toxic >0.2). Blood count 2 months prior showed Hb 10.9 g/dL, WBC $9.2x10^9$/L, platelets $274x10^9$/L. MTX was stopped and leucovorin 15 mg/d (folinic acid) started. At 10 days Hb was 9.1 g/dL, WBC $13.9x10^9$/L, and platelets $351x10^9$/L. At 1 month, baseline values were attained.

DISCUSSION

MTX is a folate antimetabolite, inhibiting DNA synthesis. Actively-proliferating, bone-marrow stem cells are susceptible, even when immunomodulatory low-doses are employed. Folate supplementation was proven effective in protecting against serious adverse reactions (4), but they still pose a potential threat, including bone-marrow toxicity, and gastrointestinal, hepatic, pulmonary and dermatologic ADRs.

Our patient had methotrexate-induced pancytopenia (Naranjo adverse drug reaction probability score 8, probable ADR). Fortunately, it was diagnosed early, quickly responding to drug withdrawal and leucovorin (G-CSF was not required). Its occurrence despite concurrent folic acid administration is unusual (5) and likely related to the long treatment duration (20 months), high cumulative dose (1000 mg), older age (78 years), and especially the patient's chronic kidney disease (estimated GFR 51.3 ml/min, stage 3aCKD).

MTX toxicity in older patients has not been extensively studied. One small retrospective study of RA patients whose mean age was 78.8 years and received MTX for at least two years concluded that treatment of elderly patients was reasonably safe, although 4/33 (12%) discontinued treatment because of gastrointestinal toxicity or raised liver enzymes (6). Another study found 7.8% of haematological ADR among patients over 65, twice than in the younger patients group. But these were comprised of thrombopenia, macrocytosis, and leucopenia. There was no case of pancytopenia (7).

Currently, pancytopenia associated with low-dose methotrexate is being increasingly recognized. It remains a potentially serious ADR: in one retrospective series, 14 patients were identified and 44% died, often due to neutropenia / agranulocytosis and severe infection (8), although larger databases have reported a much lower death rate (6.3-28%) (5).

Physicians using MTX should be better aware that even relatively low doses can cause myelosuppression (common dose of MTX has been 7.5-15 mg/week, but in recent years doses of 25 mg/week are often used). Advanced age and decreasing GFR are major risk-factors, and dose adjustment in creatinine-clearance<80 ml/min is recommended (9). We believe that blood count and GFR monitoring is necessary not only in patients *commencing* MTX as the guidelines suggest, but over time. This will lead to early diagnosis of drug-induced cytopenias, reduce complications, and allow quick reversibility.

REFERENCES

1. Braun J, Rau R. An update on methotrexate. Curr Opin Rheumatol 2009; 21:216-23.
2. Morgaccva O, Furst DE. Use of MTX in the elderly and in patients with compromised renal function. Clin Exp Rheumatol 2010; 28 (Suppl. 61):S85-S94.
3. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review. Eur J Med Chem 2018; 158:502-16.
4. Morgan SL, Baggot JE. Folate supplementation during methotrexate therapy for rheumatoid arthritis. Clin Exp Rheumatol 2010; 28(5 Suppl 61):S102-9.
5. Lim AYN, Gaffney K, Scott DGI. Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. Rheumatology 2005; 44:1051-5.
6. Hirshberg B, Muszkat M, Schlezinger O, Rubinow A. Safety of low dose methotrexate in elderly patients with rheumatoid arthritis. Postgrad Med J 2000; 76:787-9.
7. Bologna C, Viu P, Jorgensen C, Sany J. Effect of age on the efficacy and tolerance of methotrexate in rheumatoid arthritis. Br J Rheumatol 1996; 35:453-7.
8. Kuitunen T, Malmstrom J, Palva E, Pettersson T. Pancytopenia induced by low-dose methotrexate. A study of the cases reported to the Finnish Adverse Drug Reaction Register from 1991 to 1999. Scand J Rheumatol 2005; 34:238-41.

9. Bressolle F, Bologna C, Kinowski JM, et al. Total and free methotrexate pharmacokinetics in elderly patients with rheumatoid arthritis. A comparison with young patients. J Rheumatol 1997; 24:1903-9.