Autoimmunity Reviews 13 (2014) 1109–1113

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Clinical characteristics and risk factors for low dose methotrexate toxicity: A cohort of 28 patients

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ARTICLE INFO

Article history:
Received 15 May 2014
Accepted 29 May 2014
Available online 27 August 2014

Keywords:
Rheumatoid arthritis
Drug toxicity
Methotrexate
Pancytopenia
Psoriasis arthritis

ABSTRACT

Objective: Low dose (10–25 mg/week) methotrexate is widely used for the management of systemic inflammatory diseases, and is considered to be relatively safe. Toxicity due to low dose MTX has been reported but is poorly characterized. We describe the clinical features, risk factors, and outcomes of low dose MTX toxicity in a large case series at our center.

Patients and methods: We conducted a retrospective case series of all adult (>18 years) patients hospitalized at Sheba Medical Center, between 2005 and 2012 for low dose MTX toxicity.

Results: We identified 28 patients (age: 70.4 ± 13.7 years, range: 33–88; 20 (71%) females) hospitalized for low dose MTX toxicity. Indications for MTX therapy included: rheumatoid arthritis (39.2%), psoriasis ± arthritis (21.5%), polymyalgia rheumatica (10.8%) and other inflammatory conditions (28.5%). Pancytopenia was the most common manifestation of low dose MTX toxicity detected in 78.5% of the patients. Potential risk factors included acute renal failure, hypoalbuminemia, concurrent use of drugs known to interact with MTX, and dose errors. Serum MTX concentrations (n = 20, mean 0.04 ± 0.07 μg/mL range: 0–0.3) did not correlate with the degree of either neutropenia (r = −0.36; p = 0.18) or thrombocytopenia (r = 0.44; p = 0.10). Seven (25%) patients died, all from pancytopenia followed by sepsis. Serum MTX concentrations did not differ between the patients who died from MTX toxicity (n = 6; mean: 0.05 ± 0.04 μg/mL) and those who survived the toxicity (n = 14 mean 0.04 ± 0.08; p = 0.45).

Conclusions: Low-dose MTX toxicity can be life threatening, mainly due to myelosuppression. There is no rationale for MTX therapeutic drug monitoring in the setting of low-dose toxicity.

Contents

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http://dx.doi.org/10.1016/j.autrev.2014.08.027
1568-9972/

1. Introduction

Methotrexate (MTX), an anti-folate, anti-neoplastic agent, is used in high dose regimens (up to 1 g per cycle), mainly for the treatment of childhood acute lymphoid leukemias, other hematological and trophoblastic malignancies [1], osteosarcomas [2], and bladder cancer [3]. Although originally developed as an anti-neoplastic agent, low dose MTX (5–25 mg/week), has been demonstrated to be highly effective to treat immune-mediated disorders such as rheumatoid arthritis (RA) [4], psoriatic arthritis (PsA) [5], inflammatory myopathies [6], asthma [7], prophylaxis against graft *versus* host disease [8] and other inflammatory conditions. Despite the new biological agents which have revolutionized the treatment of many of these conditions, MTX is still the preferred drug in many cases [9,10]. Although low dose MTX is usually well tolerated [11], mild adverse effects, usually appearing 24–48 h following the weekly dose, have been described, and are usually not life threatening. These include: gastrointestinal symptoms (nausea, dyspepsia, stomatitis, and diarrhea), dermatological symptoms (skin rashes, alopecia) and mild central nervous system symptoms (confusion, headache, difficulty in concentration) [12–14]. These are clinically relevant mainly when they result in non-compliance to treatment. Low dose MTX-induced severe adverse effects have been also described, and include major central nervous system complications [15,16], mucositis, pulmonary involvement [17], hepatotoxicity [18], and myelosuppression [19]. While renal failure predisposes for toxicity in the low dose regimen it is rarely a consequence of this treatment [20]. This is in contrast to the high dose regimen which can cause tubular toxicity with subsequent renal failure [21,22].

Low dose MTX toxicity has been mainly described in case reports and relatively small case series [13,15,18,23,24]. The largest case series to date describes 70 RA patients who developed pancytopenia of whom 17% did not recover from myelosuppression and eventually died [19]. Another case-series described 25 patients with low dose MTX-induced pancytopenia of whom 5 had died from sepsis and 2 from acute myeloid leukemia [25]. Given the scarce data regarding the clinical manifestations and potential risk factors for low dose MTX toxicity, the objectives of our study were to systematically collect all patients who have been hospitalized in a large tertiary center in Israel due to low dose MTX toxicity in an attempt to better characterize the clinical features and outcomes of this condition as well as to identify potential risk factors for this adverse event. In addition, we sought to examine whether routine monitoring of MTX serum concentration is justified in this setting.

2. Patients and methods

To identify patients treated with low dose MTX, we conducted a retrospective medical record review of discharge diagnoses and drugs dispensed of all hospitalized patients (>18 years of age) in the medical wards at the Sheba Medical Center between January 2005 and December 2012. Among all the patients treated with low dose MTX, we identified a subgroup of patients treated for immune-mediated inflammatory diseases, and who suffered from major MTX-related toxicity, determined by at least one of the following: (1) myelosuppression: white blood cell < 4000 μL together with hemoglobin < 13 g/dL and platelet count < 130,000/μL in the absence of an alternative cause for pancytopenia, (2) clinical diagnosis of mucositis, and (3) clinical diagnosis of pneumonitis (new onset of respiratory symptoms accompanied by radiological findings of lung infiltrates in the absence of an alternative diagnosis). Minor low dose MTX-related toxicity was defined by one of the following: (1) hepatotoxicity (AST ≥ *X*2 upper limit and/or ALT ≥ *X*2 upper limit), (2) gastro-intestinal symptoms including diarrhea and abdominal pain, and (3) skin rash. Renal failure was defined by calculated glomerular filtration rate (GFR) ≤ 30 mL/min/1.73 m^2. After identifying patients treated with low dose MTX and exhibiting toxicity, we reviewed their medical records to retrieve demographic data as well as MTX dose, indication for MTX therapy, laboratory results including MTX plasma concentrations, concurrent medications as well as information on therapeutic interventions and clinical outcomes. The study was approved by the institutional ethics committee.

3. Results

3.1. Baseline characteristics

We identified 28 patients treated with low dose MTX (20 females, age: 70.4 ± 13.7 years, range: 33–88) who exhibited toxicity related to this therapy and consisted the study cohort. Indications for low dose MTX therapy included: rheumatoid arthritis (11 patients, 39.2%), psoriasis with or without arthritis (6 patients, 21.4%), polymyalgia rheumatica (3 patients, 10.7%), and other immune-mediated conditions (systemic lupus erythematosus, dermatomyositis, temporal arthritis, Susac's syndrome, asthma, scleroderma, lipoid pneumonia and Crohn's disease) in 8 patients (17.8%). Mean MTX dose was 10.5 ± 4.2 mg/week (range: 5–20) (Table 1). Twenty two patients (78.5%) had no functional impairment prior to the index hospitalization, while the remaining 6 patients (21.5%), needed help in their activities of daily living (ADL), of which one suffered from moderate and 2 from severe cognitive impairment

3.2. Clinical and laboratory manifestations of low dose MTX toxicity

3.2.1. Major

Pancytopenia was the most common manifestation of low dose MTX toxicity documented in 23 (82.1%) of the patients. Among the patients with neutropenia (mean neutrophil count: 1.14 ± 0.97, range: 0.07–2.1), seven developed severe neutropenia with neutrophil counts below 500. Fifteen (53.5%) patients had oral mucositis, of which 3 had involvement of both oral mucosa and skin. MTX-induced pneumonitis was diagnosed in 5 (17.8%) patients.

3.2.2. Minor

Abnormal liver function tests (elevated ALT/AST) were recorded in 8 (28.5%) patients. Seven (25%) patients experienced gastro-intestinal symptoms, most commonly diarrhea (6 patients) and abdominal pain (1 patient). Three patients (10.7%) had dermatological manifestations. Systemic fever was noticed in 12 (42.8%) patients

3.3. Risk factors for low-dose MTX toxicity

Hypoalbuminemia (mean: 2.60 ± 0.65 g%) was noted in 22 (78%) out of 28 patients of whom only 5 suffered from hypoalbuminemia prior to their hospitalization. Albumin levels did not differ between the patients who recovered from MTX toxicity (n = 17, 2.8 ± 0.65 g%) and those who eventually died (n = 7; 2.1 ± 0.4 g%; p = 0.28). Concomitant use of drugs known to enhance MTX toxicity was recorded in 14 patients the majority of whom have used omeprazole (n = 11) followed by non-steroidal anti-inflammatory drugs (n = 6). Four patients used omeprazole together with a non-steroidal anti-inflammatory drug and MTX (Table 2). Thirteen (46%) patients developed renal failure, 6 of