Severe pancytopenia associated with low-dose methotrexate therapy and hyperleukocytosis after filgrastim administration to a patient with subacute cutaneous Lupus Erythematosus

Jorida Kuçaj[1], Sotiraq Lako[1], Etleva Gjoshe[1], Teuta Dedej[2]

[1]American Hospital, Tirana, Albania;
[2]University Hospital Center "Mother Theresa", Tirana, Albania.

Corresponding author: Jorida Kuçaj;
Address: American Hospital, Tirana, Albania;
Telephone: +35542357535; E-mail: slako@spitaliamerikan.com

Abstract

Methotrexate is one of the most effective and widely used medications for treating rheumatic diseases. Only a few cases of severe pancytopenia caused by low-dose methotrexate therapy have been reported to date. White blood cell counts of 100,000 mm^3 or greater have been observed in 2% of patients receiving filgrastim.

We present a case of a 39-year old woman with pancytopenia, requiring hemotransfusion, folinic acid, and filgrastim, as a result of a low dose of methotrexate for subacute cutaneous Lupus Erythematosus. After five days on filgrastim treatment, the leukocyte count increased to 115,000 mm^3, and recovered completely within eight weeks.

Patients receiving low-dose methotrexate therapy require regular monitoring though a complete blood count to identify myelosuppression and avoid pancytopenia. Hyperleukocytosis from filgrastim occurs occasionally, but there is the risk of leukostasis and monitoring of the complete blood count should also be done after treatment with growth factors.

Keywords: filgrastim, methotrexate, pancytopenia.

Introduction

Severe pancytopenia is a rare adverse effect of low-dose oral methotrexate (MTX) therapy. MTX is an inhibitor of cellular proliferation, and cells with the highest turnover are most susceptible to its effect. As a consequence, when a patient's myeloproliferative cells are affected, cytopenia develops (1).

Pancytopenia is defined as the reduction of all the three formed elements of blood below the normal reference range, leading to anemia, leucopenia, and thrombocytopenia. According to the National Cancer Institute-Common Terminology Criteria for Adverse Events of severity, pancytopenia is defined as hemoglobin (Hb) <12 gr/dl (female), white blood cell count (WBC) <4,000 mm^3, absolute neutrophil count (ANC) <2,000 mm^3, platelet count (PLT) <144,000 mm^3. Severe pancytopenia is defined as Hb <8 gr/dl, WBC <2,000 mm^3, ANC <1,000 mm^3, PLT <50,000 mm^3 ($\geq$ grade 3 of myelotoxicity). Hyperleukocytosis is defined as a peripheral blood leukocyte count exceeding 100,000 mm^3.

We present a case of a woman with severe pancytopenia, associated with low-dose MTX therapy, and hyperleukocytosis after filgrastim treatment.

Case Report

A 39-year old woman with a four-year history of Subacute Cutaneous Lupus Erythematosus had been treated previously with glucocorticoids, followed by hydroxychloroquine, low-dose MTX 7.5 mg/week (cumulative dose of 530 mg) and folic acid. Complete blood count (CBC), liver and kidney function tests were performed every 3 months. Previous CBC (from 3 months ago), indicated a hemoglobin level of 11.7 gr/dl, mean corpuscular volume (MCV) 103.2 fl, WBC 3,910 mm^3, and PLT 182,000 mm^3.

The patient presented in the hospital for a routine checkup. She complained of general fatigue, without fever, and active bleeding. Upon initial examination, pallor and several painful lesions in her oral mucosa were observed. There was no evidence of hepatosplenomegaly or hemorrhagic purpura. The last dose of MTX was 5 days prior.

Laboratory studies revealed a hemoglobin level of 8.8 g/dL, MCV 97.7 fL, WBC 1,200 mm^3, ANC 570 mm^3, PLT 37,000 mm^3. Erythrosedimentation 70 mm/h, creatinine 1.58 mg/dL, azotemia 91.1 mg/dL, total bilirubin 1.09 mg/dL, SGOT 32.5 IU/L, SGPT 64.3 IU/L. Bone-marrow aspiration was hypocellular and mild megaloblastic changes were observed.

Severe pancytopenia was found at admission and after 2 days the nadir of WBC count was 770 mm^3, with an ANC of 270 mm^3, a hemoglobin level of 6.4 gr/dL, and platelet count of 16,000 mm^3.

Given her near normal CBC three months prior to admission (mild macrocytic anemia and leukopenia), and based on the above clinical and laboratory findings we were suspicious of MTX induced myelosuppression.

The patient was initially administered an intravenous leucovorin calcium 15 mg/m^2 every hours hours for two days and then every eight hours on the third day. She was given five µg/kg of filgrastim, administered subcutaneously daily and stopped after five days, when the leukocyte count reached >4,000 mm^3 (4,370 mm^3). She was also supported by transfusions of platelets, two units of PRBC, methylprednisolone 60 mg/day, empiric antibiotics and oral antifungal therapy.

During the hospital stay she complained of fatigue, sore throat, but she had no fever. On examination, she had only a few ecchymosis of the legs and buttocks. She improved significantly. The ulcerated oral lesions began to heal within four days and complete healing occurred after seven days. The treatment continued with oral calcium folinate 15 mg/day, and dose of glucocorticoids was reduced to a low-dose. Pancytopenia resolved with almost normal hematologic parameters in the two weeks of follow-up, except for the leukocyte count.

The WBC count increased to 26,600 mm^3 within 1 day of interruption of filgrastim, to 33,570 mm^3 on

the second day, 76,290 mm^3 on the third day, 98,360 mm^3 on the fifth day, and on the eighth day from stopping filgrastim it reached the peak of 115,560 mm^3. After this value, without any specific treatment, the leukocyte count fell to 74,770 mm^3 two days later, and continued to decrease.

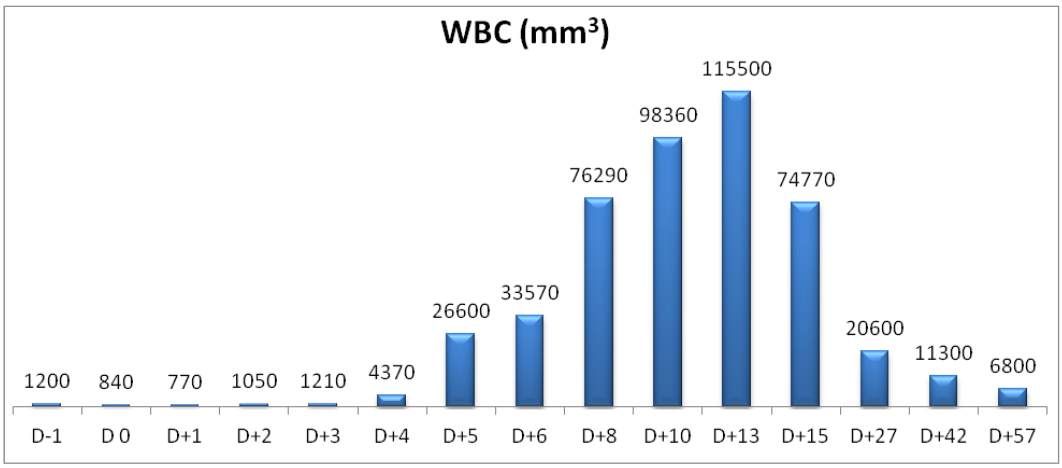
Fifteen days from admission the Hb and PLT increased up to 11.0 gr/dL and 377,000 mm^3, respectively.

The clinical status of the patient was good, without specific complaints. The patient left the hospital with low-dose prednisone, hydroxychloroquine 200 mg/day, oral calcium folinate 15 mg/day, and continued monitoring of the CBC, at first every three days and later every week.

Six weeks from the diagnosis the WBC count reached 11,300 mm^3, whereas Hb and PLT were 13 gr/dL and 162,000 mm^3, respectively. SGOT and SGPT were normal, whereas creatinemia had a value of 1.31 mg/dl. Two weeks later (eight weeks from the diagnosis), the CBC was completely normal. We had not started MTX treatment yet.

Alterations of the WBC count are presented in Figure 1.

Figure 1. Alterations of the White Blood Cells (WBC) count in our patient



Discussion

Methotrexate is a very commonly used medication to treat rheumatic diseases. Hematological effects are also seen with long-term MTX use, suggesting a cumulative effect.

Buhroo et al. (2) in their study evaluated that 11.8% of patients with long term MTX use, had hematological side effects. Different studies have given different results, ranging from 3% to 25% (3,4). These effects are generally mild leucopenia, thrombocytopenia, megaloblastic anemia, and pancytopenia and mostly occur in patients with diminished folate stores. Elevation of MCV usually precedes the occurrence of hematological toxicity. Folate supplementation is sufficient for most of patients (5,6).

Pancytopenia is not an uncommon side effect of low-dose MTX therapy in rheumatic diseases. It can lead to serious complications, including death. Severe pancytopenia associated with low-dose MTX therapy is a potentially serious complication that may occur at any time during therapy. Clinically significant pancytopenia was found in 1% to 2% of Rheumatoid Arthritits patients on MTX therapy (7,8). Lim et al. (9) estimate the prevalence of methotrexate-induced pancytopenia in their cohort to be approximately 1.9%. They suggest that pancytopenia caused by methotrexate is underestimated. This adverse effect is more likely

to occur in patients with renal dysfunction, hypoalbuminemia, low folate levels, concomitant infection, advanced age, concomitant use of drugs, and lack of folate supplementation as risk factors (10). Gastrointestinal mucositis and myelosuppression are primary toxic effects of methotrexate. The mucosal cells are more sensitive to methotrexate than the precursor cells in the bone marrow because of greater accumulation and persistence of methotrexate in the intestinal epithelium. Mucositis usually appears 3-7 days after the drug administration and precedes the onset of leucocyte and platelet count precipitation by several days (11). Carmichael et al. (12) in their study noted that hydroxychloroquine alters the pharmacokinetics of methotrexate; there is slower clearance and uptake with a greater area under the curve for methotrexate in patients taking the combination; this interaction may account for the greater efficacy of the combination of hydroxychloroquine and methotrexate than methotrexate alone Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. Extra vigilance for MTX adverse effects during combination therapy with hydroxychloroquine is recommended, especially if renal function is known to be decreased.

In our patient, risk factors for pancytopenia such as renal insufficiency, low folate levels and concomitant use of drugs were identified. In the CBC of three months ago, the patient had mild macrocytic anemia and leukopenia and some days before the diagnosis of pancytopenia she complained about oral mucositis. Furthermore, she had mild renal impairment and used concomitant hydroxychloroquine.

Conflicts of interest: None declared.

Bone marrow recovery typically occurs within two weeks after the withdrawal of MTX and responds to folinic acid administration.

In our case, we used folinic acid, filgrastim (G-CSF analog) to stimulate the proliferation and differentiation of granulocytes until bone marrow recovery. Pancytopenia resolved with almost normal hematologic parameters in the two weeks of follow-up, except for the leukocyte count.

According to the Food and Drug Administration (FDA) prescribing information, WBC equal to or greater than 100,000 mm^3, without evidence of adverse effects, have occurred in 2% of patients using Filgrastim.

In our patient, after five days of filgrastim treatment the WBC count increased to 26,600 mm^3 and eight days from the stopping of filgrastim it reached the peak of 115,560 mm^3. After this value without any specific treatment, the leukocyte count fell to 74,770 mm^3 two days later, and recovered completely in eight weeks from the diagnosis.

Severe pancytopenia associated with low-dose MTX therapy, and hyperleukocytosis after filgrastim treatment in the same patient had, to our knowledge, not been previously reported.

Conclusions

Patients receiving low-dose methotrexate therapy require regular monitoring for bone marrow injury, especially those who have risk factors for possible methotrexate toxicity. Regular monitoring through CBC helps to identify myelosuppression and avoid pancytopenia. Hyperleukocytosis from filgrastim occurs occasionally, but there is the risk of leukostasis and complete blood count should also be monitored after treatment with growth factors.

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