Low-Dose Methotrexate-induced Severe Pancytopenia in One Patient with Psoriasis Undergoing Hemodialysis

Hsiu-Hui Chiu  Wen-Yu Chang  Gwo-Shing Chen

A 54-year-old male with psoriasis for about 40 years admitted due to psoriatic erythroderma. He was also a victim of diabetic mellitus and uremia undergoing hemodialysis (HD) for about two years. Besides, he took folic acid 5 mg per day for years because of macrocytic anemia. Tracing back his history, he was treated at our clinic for about 30 years and received methotrexate (MTX) treatment many times in the past 30 years before renal function was deteriorated. No serious complication was noted. Blood examination on admission showed hemoglobin (Hgb) 12.9 g/dl (12-16), mean corpuscular volume (MCV) 102.0 fl (79.9-101.0), white blood count (WBC) 14.08 × 10³/µl (4.0-10.0), with 77.3% of neutrophils (37-75), 4.3% of eosinophils (0-4), platelet (PLT) 278 × 10³/µl (130-500), blood urea nitrogen (BUN) 26.2 mg/dl (7.0-18.0), creatinine 8.73 mg/dl (0.6-1.3), albumin 2.97 gm/dl (3.5-5.0), C-reactive protein (CRP) 12.9 µg/ml (<5). MTX therapy as 5 mg (2.5 mg/tab, 2 tablets) per 12 hours, 3 times per week was started. Six days later, severe mucositis was noted. (Fig. 1) On the next day, leukopenia (WBC = 1.67 × 10³/µl with 72.4% of neutrophils, 5.4% of eosinophils), thrombocytopenia (PLT = 113 × 10³/µl) and elevated CRP 38 µg/ml were noted and MTX therapy was terminated. The cumulative dose of MTX was 15 mg. Three days later, he developed chills and followed by fever up to 37.8°C. Pancytopenia, relative hypereosinophilia and increasing CRP were noted. (WBC 0.95 × 10³/µl with 60% of neutrophils, 10.5% of eosinophils, Hgb 9.5 g/dl, PLT 28 × 10³/µl, CRP 52.3 µg/ml). Neutropenic fever was diagnosed and broad spectrum antibiotics were administrated. The nadir of WBC count was 0.67 × 10³/µl with 14.9% eosinophils on 11th day. On 12th day, granulocyte-colony-stimulating factor (GCSF) was given 300 mcg subcutaneously per day for three days. Hematologic recovery was noted after three
doses of GCSF treatment (WBC 9.11×10^9/µl, Hgb 9.8 g/dl, PLT 154×10^9/µl) and fever subsided.

These findings supported the diagnosis of low-dose MTX-induced severe pancytopenia with neutropenic fever. MTX is approved by the US FDA for severe psoriasis in 1971. Severe adverse effects of low-dose MTX (<30mg weekly) are relatively rare. Pancytopenia is a rare and serious adverse effect, occurring in 2.5-3% of patients. The mortality rate is 44%. The most frequent cause of death is infection. The risk factors for MTX-induced pancytopenia are impaired renal function, hypoalbuminemia, increased age, pre-existing infection, possible drug interactions, increasing MCV values. Since excretion of MTX is almost entirely renal through glomerular filtration and proximal tubular secretion, within 12-24 hours of a dose, 50-80% of MTX is excreted unchanged in the urine, some authors believed that impaired renal function is the most important cause of MTX accumulation and toxicity. In general population, the duration of MTX used to develop pancytopenia was variable. The median duration is 36 months. The median dose of MTX is 12.5 mg/week. Till now very few cases of severe pancytopenia caused by low-dose MTX therapy have been reported in chronic uremic patient undergoing dialysis. Surprisingly, the duration of MTX used to develop pancytopenia was much shorter, often within 1-2 weeks. And in most cases the cumulative doses were extremely low, even as low as single dose of 2.5 mg MTX. Idiosyncratic reaction cannot be ruled out in these cases developing pancytopenia after low dose of MTX. However, our patient had taken MTX many times before HD and no serious complication was noted. This is his first time to take MTX after undergoing HD and pancytopenia occurred after cumulative dose 15mg of MTX. There can be little doubt that the impaired clearance of the drug is responsible for toxicity. The reasonable explanation is that MTX is poorly cleared with HD so administration of MTX in HD patients seems equivalent to continuous infusion of the drug.

In our case, hypoalbuminemia and increasing MCV are additional risk factors. Hypoalbuminemia causes a decreased binding ratio and increases toxicity. In addition, hypoalbuminemia leads to extravascular fluid accumulations, such as pleural effusions and ascites. This extracellular fluid serves as a reservoir from which drug is slowly released. Increasing MCV may suggest underlying folate deficiency. In clinical practice, supplementation with folic acid (1 mg/day) or folinic acid (2.5 mg/week) should be considered in all patients taking MTX, especially in those patients with a MCV>10. Neither low-dose folic acid nor folinic acid interferes with the beneficial effect of MTX.

If patients develop pancytopenia, discontinuation of MTX and intravenous leucovorin (LV) rescue within 24 hours (10-20 mg every 6 hours) should be started until the blood MTX level becomes undetectable, or until peripheral WBC and PLT counts return to normal. Since low-dose MTX induced pancytopenia is rare, LV rescue is not prescribed routinely. When pancytopenia is noted, the interval between MTX administration is always longer than 24 hours. Reviewing the literature, LV rescue was prescribed in some cases. Till now, there is no study to compare if there is significant difference in the prognosis. Because the reversal of
MTX by LV is competitive, we propose that the effect of LV rescue after 24 hours is limited. HD with high flux membrane can efficiently reduce the serum level of MTX, but cannot remove the polyglutamated MTX metabolite within cells. Peritoneal dialysis is reported ineffective at reducing serum level of MTX. MTX is also poorly cleared by HD; however, clearance through HD is greater then by peritoneal dialysis. Both GCSF and methylprednisolone have benefits in the recovery of MTX-induced pancytopenia.

Since there is no dosing recommendation for low-dose MTX therapy in dialysis patients as yet and it may lead to deleterious and irreversible consequences, including death, sharing the opinion expressed by Nakamura et al., Basile et al., Ellman et al. and Chatham et al., we recommended not prescribing MTX to dialysis patients.

REFERENCES