Clinical Dilemma Over Low-dose Methotrexate Therapy in Dialysis Patients

A Case report and Review of Literature

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Myelosuppression is the life-threatening adverse effect of methotrexate. Impaired kidney function is a major aggravating factor of methotrexate-induced myelosuppression. In end-stage renal disease patients, methotrexate therapy must be with cautious because the efficacy of removal of methotrexate by means of dialysis is in doubt. In clinical practice, low-dose methotrexate is still used by clinicians in treatment of dialysis patients with immunological disorders. We reported a 61-year-old woman on continued ambulatory peritoneal dialysis who developed pancytopenia with a nadir leukocyte count of 0.03×10^9/L, leading to severe sepsis after 3 doses of methotrexate, 7.5 mg weekly. We highlighted that methotrexate therapy in dialysis patients, even with low doses could impose the risk of myelosuppression, causing a fatal outcome. Alternative medications to methotrexate might be recommended in dialysis patients.

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INTRODUCTION

Methotrexate, an antimetabolite immunosuppressant, is a mainstay treatment for autoimmune diseases, in low weekly doses.[1-2] However, side effects of methotrexate, especially myelosuppression, could cause significant morbidity and mortality.[3,4] Risk factors such as impaired kidney function, advanced age, diabetes mellitus, folic acid deficiency, and hypoalbuminemia contribute to the frequency and severity of bone marrow toxicity following low-dose methotrexate therapy.[5]

Application of low-dose methotrexate in uremic patients on maintenance hemodialysis or continued ambulatory peritoneal dialysis (CAPD) is still controversial. We presented low-dose methotrexate-induced severe pancytopenia in a CAPD patient.

CASE REPORT

A 61-year-old woman with end-stage renal disease was presented with a 3-day history of general malaise and stomatitis to our rheumatologic clinic. She had been on maintenance CAPD for 6 years. One month before admission, methotrexate, 7.5 mg weekly, had been started for intractable chronic eczema. Her baseline leukocyte count was 8.94×10^9/L (reference range, 4.5×10^9/L to 11.0×10^9/L). After 2 doses of weekly methotrexate, her skin lesions had dramatically improved. The follow-up leukocyte count was 4.28×10^9/L.

Physical examination showed an oral body temperature of 40.4°C, a pulse rate of 122 beats per minute, and multiple oral mucositis. Laboratory analysis revealed the following: leukocyte count, 0.03×10^9/L; hemoglobin level, 5.0 g/dL; platelet count, 27.0×10^9/L (reference range, 150×10^9/L to 400×10^9/L); C-reactive protein, 27.62 mg/dL (reference, < 0.5 mg/dL); and the serum methotrexate, 0.08 µmol/L (reference, < 0.02 µmol/L).

Methicillin-resistant *Staphylococcus aureus* was identified from blood culture, 3 days after

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admission. The patient was isolated. Methotrexate was discontinued while the antidote with folinate was started. The granulocyte colony-stimulating factor was administered until recovery of leukocyte count. Packed erythrocytes and platelet concentrates were transfused. Empiric antibiotics with cefepime and vancomycin were administered. Continued ambulatory peritoneal dialysis was persistently performed. Eleven days after admission, fever subsided. The serum methotrexate was undetectable and the leukocyte count increased to 11.99 × 10^9/L. Twenty-four days after admission, the patient fully recovered and discharged.

DISCUSSION

Methotrexate therapy could bring about fatal adverse effect rather than therapeutic benefits in dialysis patients, even in low dose. To strengthen understandings of low-dose methotrexate-induced myelosupression in dialysis patients, several important issues were clarified. From PubMed search of dialysis patients with pancytopenia after low-dose methotrexate therapy, 16 patients were recognized,[7-18] which are summarized in Table 1. These 16 cases were published between 1990 and 2012, meaning that in dialysis patients, the potential high risk of low-dose methotrexate was not well known or lethal myelosuppression attributed to low-dose methotrexate had not been expected by clinicians.

We first made a comparison on clinical outcome in low-dose methotrexate-induced pancytopenia between nondialysis and dialysis patients. In nondialysis patients, Gutierrez-Urena and colleagues demonstrated the mortality rate was 17.1%.[5] Lim and coworkers demonstrated the median age was 76 years; median dose was 12.5 mg weekly; median therapeutic duration was 36 months; and 10 of 25 had leukocyte count lower than 2 × 10^9/L. The mortality rate was 28%. The 16 dialysis patients reported in the literature had a median age of 58.5 years and mean cumulative doses of 17 mg. The median dose was 5 mg weekly and median therapeutic duration was 2 weeks. Fifteen of 16 had leukocyte lower than 2 × 10^9/L. The mortality rate was 43.8%. Taken together, the dialysis patients were relatively young, had a short dosing duration, low cumulative doses, and severe leukopenia in contrast to those of nondialysis patients. The fatal outcome was pointed out in dialysis patients.

Table 1. Clinical Data of Methotrexate-induced Myelosuppression in Dialysis Patients*

Reference	Sex	Age	Dialysis Modality	Indication	Dose, mg/wk	Duration, wk	Cumulative Dose, mg	Serum Methotrexate, µmol/L	Nadir Leukocyte count, × 10^9/L	Outcome
Diskin et al[7]	Male	60	PD	RA	10.0	2	20.0	0.53	0.3	Deceased
Chess et al[8]	Male	64	PD	Psoriasis	…	…	35.0	…	0.3	Deceased
Sun et al[9]	Female	33	PD	LA	5.0 7.5	2 2	25.0	…	0.6	Recovered
Present study	Female	61	PD	Eczema	7.5	3	22.5	0.08	0.03	Recovered
Ellman and Ginsberg[10]	Female	52	Hemodialysis	RA	2.5	Single Dose	2.5	0.13	0.5	Deceased
Ellman and Ginsberg[10]	Female	47	Hemodialysis	SS	2.5	Single Dose	2.5	…	1.5	Recovered
Nakamura et al[11]	Male	57	Hemodialysis	RA	5.0	Single Dose	5.0	0.03	0.1	Recovered
Chatham et al[12]	Male	49	Hemodialysis	Myositis	…	2	…	…	0.09	Recovered
Chatham et al[12]	Male	52	Hemodialysis	Myositis	5.0	Single Dose	5.0	…	2.2	Recovered
Chatham et al[12]	Female	61	Hemodialysis	Psoriasis	2.5	3	7.5	…	0.05	Deceased
Boulanger et al[13]	Female	60	Hemodialysis	RA	5.0	2	10.0	…	1.3	Recovered
Basile et al[14]	Female	74	Hemodialysis	RA	5.0	2	10.0	…	1.7	Recovered
Boey et al[15]	Male	66	Hemodialysis	Psoriasis	5.0	2	10.0	0.03	0.07	Recovered
Yang et al[16]	Female	55	Hemodialysis	RA	7.5	12	90.0	0.11	0.4	Deceased
Seneschal et al[17]	Male	76	Hemodialysis	BP	5.0	1.5	7.5	0.47	0.55	Deceased
Cheung et al[18]	Male	56	Hemodialysis	Psoriasis	2.5	Single Dose	2.5	0.06	0.06	Deceased

*PD indicates peritoneal dialysis; RA, rheumatoid arthritis; LA, lupus arthritis; SS, systemic sclerosis; and BP, bullous pemphigoid. Ellipses indicate data not available.

The 16 dialysis patients developed similar complications, but the final outcome was different. Of 16 patients, serum methotrexate level was obtained from 8 patients. The mean nadir leukocyte count, mean methotrexate level, and outcome for these patients are listed in Table 2. Those who died had lower nadir leukocyte counts and higher methotrexate levels than those who recovered with. It might be assumed the highest methotrexate level indicated more serious bone marrow toxicity, causing the lowest leukocyte count and finally a poor outcome. However, data are limited. Clinical outcome is also affected by a variety of factors including underlying risk factors, cumulative doses, methotrexate clearance, early detection, and comprehensive medical care.

Whether CAPD patients are more prone to myelosuppression than hemodialysis patients with low-dose methotrexate is yet to be determined. The efficacy of removal of methotrexate by means of dialysis was associated with methotrexate toxicity. Diskin and coworkers reported that the clearance of methotrexate on CAPD was less effective than that on hemodialysis.[7] In the currently available data, the mean methotrexate level in the 2 CAPD cases is 0.3 µmol/L, which is higher than that of 6 hemodialysis patients (0.14 µmol/L). Recent reports suggested that intensive-cycler CAPD and high-flux hemodialysis were potential options for effective removal of methotrexate.[19] Further studies are required to confirm whether such dialysis methods could prevent and correct bone marrow toxicity arising from methotrexate.

In conclusion, application of low-dose methotrexate therapy in dialysis patients is a clinical dilemma. Despite therapeutic benefits, we emphasize that dialysis patients have a high risk and have more fatal outcome with low-dose methotrexate-induced myelosuppression, as compared with other patients. Alternative medication to methotrexate might be recommended in dialysis patients.

Table 2. Mean Nadir Leukocyte Count and Mean Serum Methotrexate Level by Clinical Outcome in Dialysis Patients with Myelosuppression After Low-dose Methotrexate*

Parameters	Clinical Outcome	
	Deceased	Recovered
Mean nadir leukocyte, × 10^9/L (n = 16)	0.31 (n = 7)	0.85 (n = 9)
Mean serum methotrexate, µmol/L (n = 8)	0.26 (n = 5)	0.05 (n = 3)

*Summary of data reported for 16 patients in the literature[7-18]

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009;68:1094-9.
2. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009;60:824-37.
3. Sandoval DM, Alarcón GS, Morgan SL. Adverse events in methotrexate-treated rheumatoid arthritis patients. Br J Rheumatol. 1995;34:49-56.
4. Lim AY, Gaffney K, Scott DG. Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. Rheumatology. 2005;44:1051-5.
5. Gutierrez-Ureña S, Molina JF, García CO, Cuéllar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum. 1996;39:272-6.
6. Al-Hasani H, Roussou E. Methotrexate for rheumatoid arthritis patients who are on hemodialysis. Rheumatol Int. 2011;31:1545–7.
7. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. Removal of methotrexate by peritoneal dialysis and hemodialysis in a single patient with end-stage renal disease. Am J Med Sci. 2006;332:156-8.
8. Chess JA, Scholey G, Mikhail AI. Neutropenia associated with the use of low-dose methotrexate in a peritoneal dialysis patient. Nephrol Dial Transplant. 2004;19:2158-9.
9. Sun CY, Lin HC, Chen YC, Tsai CR, Wu MS. Leukemoid reaction after methotrexate-induced pancytopenia in a patient undergoing continuous ambulatory peritoneal dialysis. Chang Gung Med J. 2006;29:513-7.
10. Ellman MH, Ginsberg D. Low-dose methotrexate and severe neutropenia in patients undergoing renal dialysis. Arthritis Rheum. 1990;33:1060-1.
11. Nakamura M, Sakemi T, Nagasawa K. Severe pancytopenia caused by a single administration of low dose methotrexate in a patient undergoing hemodialysis. J Rheumatol. 1999;26:1424-5.
12. Chatham WW, Morgan SL, Alarcón GS. Renal failure: a risk factor for methotrexate toxicity. Arthritis Rheum. 2000;43:1185-6.
13. Boulanger H, Launary-Vacher V, Hierniaux P, Fau JB, Deray G. Severe methotrexate intoxication in a hemodialysis patient treated for rheumatoid arthritis.

Nephrol Dial Transplant. 2011;16:1087.

14. Basile C, Montnaro A, Semetaro A. Should low dose methotrexate therapy be prescribed to dialysis patients? Nephrol Dial Transplant. 2002;17:530-1.
15. Boey O, Van Hooland S, Woestenburg A, Van der Niepen P, Verbeelen D. Methotrexate should not be used for patients with end-stage kidney disease. Acta Clin Belg. 2006;61:166-9.
16. Yang CP, Kuo MC, Guh JY, Chen HC. Pancytopenia after low dose methotrexate therapy in a hemodialysis patient: case report and review of literature. Ren Fail. 2006;28:95-7.
17. Seneschal J, Héliot-Hostein I, Taieb A. Pancytopenia induced by low-dose methotrexate in a haemodialysis patient treated for bullous pemphigoid. J Eur Acad Dermatol Venereol. 2007;21:1135-6.
18. Cheung KK, Chow KM, Szeto CC, Tai MH, Kwan BC, Li PK. Fatal pancytopenia in a hemodialysis patient after treatment with low-dose methotrexate. J Clin Rheumatol. 2009;15:177-80.
19. Murashima M, Adamski J, Milone MC, Shaw L, Tsai DE, Bloom RD. Methotrexate Clearance by High-Flux Hemodialysis and Peritoneal Dialysis: A Case Report. Am J Kidney Dis. 2009;53:871-4.

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