Clinical Dilemma Over Low-dose Methotrexate Therapy in Dialysis Patients
A Case report and Review of Literature

Wen-Cheng Liu,1 Hsiang-Cheng Chen,2 Jin-Shuen Chen3

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 × 10⁹/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.

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 × 10⁹/L (reference range, 4.5 × 10⁹/L to 11.0 × 10⁹/L). After 2 doses of weekly methotrexate, her skin lesions had dramatically improved. The follow-up leukocyte count was 4.28 × 10⁹/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 × 10⁹/L; hemoglobin level, 5.0 g/dL; platelet count, 27.0 × 10⁹/L (reference range, 150 × 10⁹/L to 400 × 10⁹/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...
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 $11.99 \times 10^9$/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 myelosuppression 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 $2 \times 10^9$/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 $2 \times 10^9$/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*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>Dialysis Modality</th>
<th>Indication</th>
<th>Dose, mg/wk Duration, wk</th>
<th>Cumulative Dose, mg</th>
<th>Serum Methotrexate, μmol/L</th>
<th>Nadir Leukocyte count, × 10^9/L</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diskin et al,7</td>
<td>Male</td>
<td>60</td>
<td>PD</td>
<td>RA</td>
<td>10.0</td>
<td>0.0</td>
<td>0.3</td>
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<td></td>
</tr>
<tr>
<td>Chess et al,8</td>
<td>Male</td>
<td>64</td>
<td>PD</td>
<td>Psoriasis</td>
<td>5.0</td>
<td>0.6</td>
<td>0.03</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Sun et al,9</td>
<td>Female</td>
<td>33</td>
<td>PD</td>
<td>LA</td>
<td>5.0</td>
<td>2.5</td>
<td>25.0</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Present Study</td>
<td>Female</td>
<td>61</td>
<td>PD</td>
<td>Eczema</td>
<td>7.5</td>
<td>3</td>
<td>22.5</td>
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</tr>
<tr>
<td>Ellman and Ginsberg10</td>
<td>Female</td>
<td>61</td>
<td>PD</td>
<td>Psoriasis</td>
<td>5.2</td>
<td>0.08</td>
<td>0.3</td>
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<tr>
<td>Ellman and Ginsberg10</td>
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<td>52</td>
<td>PD</td>
<td>RA</td>
<td>5.0</td>
<td>0.13</td>
<td>1.5</td>
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<tr>
<td>Ellman and Ginsberg10</td>
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<td>47</td>
<td>PD</td>
<td>RA</td>
<td>5.2</td>
<td>0.03</td>
<td>0.1</td>
<td>Recovered</td>
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<tr>
<td>Ellman and Ginsberg10</td>
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<td>49</td>
<td>PD</td>
<td>RA</td>
<td>5.0</td>
<td>0.09</td>
<td>0.03</td>
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<tr>
<td>Chatham et al12</td>
<td>Male</td>
<td>49</td>
<td>Hemodialysis</td>
<td>Myelitis</td>
<td>5.0</td>
<td>5.0</td>
<td>7.5</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Chatham et al12</td>
<td>Male</td>
<td>52</td>
<td>Hemodialysis</td>
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<td>5.0</td>
<td>2.5</td>
<td>7.5</td>
<td>Recovered</td>
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<td>Chatham et al12</td>
<td>Male</td>
<td>60</td>
<td>PD</td>
<td>Myositis</td>
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<tr>
<td>Basile et al14</td>
<td>Female</td>
<td>60</td>
<td>PD</td>
<td>RA</td>
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<td>0.05</td>
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<tr>
<td>Basile et al14</td>
<td>Female</td>
<td>66</td>
<td>PD</td>
<td>RA</td>
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<td>0.47</td>
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<tr>
<td>Yang et al16</td>
<td>Female</td>
<td>55</td>
<td>PD</td>
<td>RA</td>
<td>7.5</td>
<td>0.11</td>
<td>0.47</td>
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<tr>
<td>Seneschal et al17</td>
<td>Male</td>
<td>76</td>
<td>PD</td>
<td>BP</td>
<td>5.0</td>
<td>0.06</td>
<td>0.06</td>
<td>Recovered</td>
<td></td>
</tr>
</tbody>
</table>

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

www.SID.ir
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. 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. 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.

ACKNOWLEDGEMENTS
We thank the patient for kindly consenting to publish the clinical information.

CONFlict OF INTEREST
None declared.

REFERENCES

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Clinical Outcome</th>
<th>Deceased</th>
<th>Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean nadir leukocyte, × 10^9/L (n = 16)</td>
<td>0.31 (n = 7)</td>
<td>0.85 (n = 9)</td>
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<tr>
<td>Mean serum methotrexate, μmol/L (n = 8)</td>
<td>0.26 (n = 5)</td>
<td>0.05 (n = 3)</td>
<td></td>
</tr>
</tbody>
</table>

*Summary of data reported for 16 patients in the literature7-18


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