



## Development of Pancytopenia After Single Low-Dose Methotrexate Therapy in Patients with Chronic Kidney Disease: a Review of the Literature

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### Abstract

Methotrexate (MTX) is widely used in the treatment of both rheumatoid arthritis (RA) and psoriatic arthritis (PA) with a side effect of pancytopenia. However, very few cases of severe pancytopenia caused by low-dose MTX therapy have been described in chronic kidney disease. Pancytopenia occurred after using a single dose of MTX in our three patients with chronic kidney dysfunction. While one patient died due to sepsis and multiple organ failure, the others recovered. The severity of MTX-induced pancytopenia in our cases was likely related to the underlying kidney disease. These cases suggest that uremic patients may develop severe fatal bone marrow toxicity even with a single dose of MTX. Therefore, complete blood count monitoring after MTX treatment in this population would be beneficial.

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### Introduction

Methotrexate (MTX), a classical antifolate, has gained wide acceptance due to its efficacy in a variety of inflammatory rheumatological disorders, including rheumatoid arthritis (RA) and psoriatic arthritis (PA).<sup>1,2</sup> Although MTX at doses as low as 5-25 mg per week is the first-line therapy for RA, inter- and intra-patient variability in the response to treatment with the contribution of variability in concentrations of active polyglutamate metabolites can affect clinical efficacy and toxicity.<sup>3</sup> The absence of neutropenia

or agranulocytosis episodes with MTX treatment at a dose of 7.5 mg per week for two years in patients with RA over 65 years of age indicates that this treatment is safe even in the elderly.<sup>4</sup> However, rare adverse hematological side effects associated with low-dose MTX, including fatal pancytopenia, are an increased cause of concern in patients with rheumatological disorders and renal dysfunction.<sup>3,5</sup> Herein, three patients with chronic kidney disease (CKD) who developed pancytopenia after a single oral or intramuscular dose of MTX are presented.



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## Case Report

**Case 1.** The first case was a 58-year-old woman with a history of chronic hypertension and kidney dysfunction. She had RA for 30 years. Serum creatinine level was 1.4 mg/dL and creatinine clearance was 43 mL/min. MTX was prescribed because of insufficient effect of steroids on increased joint pain, and a single dose of 12.5 mg was administered orally. Abdominal pain, chest discomfort, vomiting, and skin rash developed 5 days after administration of single-dose MTX. Petechial lesions on her pretibial area and ecchymosis on anterior aspect of left knee were remarkable. Laboratory findings at admission included severe pancytopenia: white blood cells 1,200 cells/ $\mu$ L with 160 cells/ $\mu$ L neutrophils, platelets 8,800 cells/ $\mu$ L and hemoglobin 9.1 g/dL. A bone marrow aspiration revealed erythroid hyperplasia with megaloblastic maturation and relative preponderance of eosinophils in the granulocytic series without atypical or blastic cells, as well as marked suppression of the megakaryocytic series. The patient was diagnosed as having MTX-induced pancytopenia and myelosuppression. She was treated with folinic acid and granulocyte colony stimulating factor. Two units of red blood cells and two units of platelets were replaced. On the 13th day of her hospitalization, she recovered completely and was discharged.

**Case 2.** The second case was a 43-year-old male patient with psoriasis and PA for 20 years. He had been on hemodialysis treatment for 3 months due to end-stage renal disease. MTX was prescribed because of a diffuse psoriatic eruption, and a single dose of 12.5 mg was administered orally. 7 days after the use of MTX, the patient applied with complaints of diarrhea, anorexia, chills, fever and not feeling well for two days. In his physical examination, blood pressure was 100/60 mmHg, pulse rate was 110 beats/min, body temperature was 38.5 °C, and respiratory rate was 20/min. Laboratory findings at the admission showed pancytopenia with a hemoglobin level of 5.9 g/dL, a white blood cell count of 3,100 cells/ $\mu$ L with 590 cells/ $\mu$ L neutrophils, and a platelet count of 31,300 cells/ $\mu$ L. The patient was diagnosed as having MTX-induced pancytopenia and neutropenic sepsis. He was treated with amikacin,

cephapirin, folinic acid and granulocyte colony stimulating factor. After two days, his white blood cell dropped to 400 cells/ $\mu$ L without neutrophils. Then, the patient's need for inotropic agent and blood product transfusion continued. Eventually, the patient died with multiple organ failure due to sepsis.

**Case 3.** The third case was a 22-year-old woman patient with psoriasis for 20 years. She had been on hemodialysis treatment for 13 years due to end-stage renal disease. A dermatologist started a single dose of 10 mg intramuscular MTX therapy per week for active psoriatic lesions. Five days later, she admitted to the emergency room of our center with complaints of fever, vomiting, nausea, diarrhea, epistaxis and stomatitis. In her physical examination, blood pressure was 100/60 mmHg, pulse rate was 107 beats/min, body temperature was 39.5 °C, and she had multiple oral mucosites. Laboratory analysis revealed the following: pancytopenia, with a hemoglobin level of 5.5 g/dL, a white blood cell count of 1,810 cells/ $\mu$ L with 390 cells/ $\mu$ L neutrophils, and a platelet count of 72,000 cells/ $\mu$ L. The patient was diagnosed as having MTX-induced pancytopenia and neutropenic sepsis. She was treated with meropenem, fungostatin gargling, folinic acid and granulocyte colony stimulating factor. Due to the deepening of pancytopenia, 12 units of fresh frozen plasma, 10 units of platelet concentrate and two units of red blood cell support were required. On the 12<sup>th</sup> day of treatment, the patient's blood values improved. She was discharged on the 21<sup>st</sup> day after admission.

## Discussion

Long-term weekly low-dose MTX therapy has proven to be highly effective in RA and other rheumatic diseases. Although myelosuppression is major dose-limiting side effect of high-dose MTX, low-dose MTX therapy can infrequently cause significant side effects such as hepatotoxicity, pulmonary damage and myelosuppression.<sup>6</sup> Low-dose weekly therapy in RA can lead hematologic toxicity associated with macrocytic red blood cells due to folate depletion.<sup>7</sup> Occasionally, anemia, leukopenia or thrombocytopenia can occur even without significant reduction in other cell lines.<sup>6</sup> But, the development of pancytopenia is a more

severe complication after low-dose MTX use.<sup>8-11</sup>

A literature search found a total of 70 cases with pancytopenia related to low-dose MTX therapy in RA patients between 1980 to 1995 years.<sup>12</sup> In most patients, the mean weekly MTX dose was 7.5-10 mg and the mean cumulative dose was 675 mg (range: 10-4,800). 12 (17.1%) patients died, 10 of 12 patients had renal dysfunction and 9 had concomitant infection. The toxicity data from long-term prospective studies involving 511 patients treated with MTX for at least 13 weeks found an estimated incidence of pancytopenia of 1.4% (n=7).<sup>12</sup> In a prospective follow-up study assessed the frequency of MTX-induced pancytopenia in 157 patients with psoriasis, an overall incidence of pancytopenia was 11%.<sup>2</sup> In other study, the rate of pancytopenia was lower in 284 RA patients who received weekly oral low-dose MTX therapy (n=4, 1.4%).<sup>13</sup> The cumulative dose of MTX ranged from 15 mg to 760 mg at the time of pancytopenia. In another study, the prevalence of cytopenia was 2.38% (n=10) in 420 patients with RA, and only 1 patient had pancytopenia.<sup>14</sup> Serum creatinine values of three patients with cytopenia were higher than 1.2 mg/dL. Patients with cytopenia received MTX at a weekly dose of 2.5-8 mg for a mean of 60 months (range: 10-119).<sup>14</sup> Intriguingly, no correlation was found between the total MTX dose and the severity of side effects.<sup>2</sup> In case series of Sosin et al.<sup>15</sup>, MTX doses and durations of four cases with myelosuppression were 17.5 mg for 2 months, 5 mg for 6 months, 5 mg for 10 years and 10 mg for 7 months. Similarly, one of Calvo-Romero's<sup>16</sup> 2 patients who developed MTX-related pancytopenia used 15 mg of MTX for 10 days and the other used 1,030 mg of MTX for 23 months. A total of five patients of around 2,500 patients of RA who prescribed MTX between January 1996 to September 2005 developed MTX-induced pancytopenia, and the cumulative dose of MTX of patients varied from 25 mg to 2.1 g.<sup>17</sup> Several patients developed fatal pancytopenia even after the minimal cumulative dose of MTX as low as 10 mg, and may occur at any time during treatment.<sup>12</sup> In another report, the minimal single MTX dose leading to fatal neutropenia in patients with chronic uraemia had been reported to be 2.5 mg per week.<sup>18</sup>

After starting MTX therapy, pancytopenia may occur suddenly within 1-2 months with a possible idiosyncratic reaction or years later due to dose-

dependent cumulative effect.<sup>19</sup> Myelosuppression can be due to impaired MTX excretion and/or accumulation of its metabolites intracellularly. Numerous riskfactors for MTX-induced pancytopenia include impaired renal function, hypoalbuminemia, low folate levels, concurrent infection, advanced age, multiple drugs usage and lack of folate supplementation.<sup>20</sup> Previous studies have shown association of cytopenia with C677T and 1298AA polymorphism.<sup>21,22</sup>

Considering the literature data, it is clear that presence of renal dysfunction is the most important risk factor of MTX toxicity including hematological effects.<sup>5,12,23</sup> Renal impairment rates in patients with pancytopenia in different series have been reported between 30.4% and 54.3%.<sup>12,24,25</sup> Approximately 35% of MTX is bound to plasma proteins. It is mainly cleared through the kidneys and is excreted 80% to 90% of the absorbed amount is excreted in the urine unchanged within 48 hours by glomerular filtration and active tubular secretion, mostly within the first 8 hours.<sup>1,3,5</sup> Therefore, impaired renal excretion of MTX and prolonged exposure to the drug increase the risk of myelosuppression and other toxicities. If occurrence of an acute disease or addition or change of a non-steroidal anti-inflammatory drug (NSAID) impair renal function or MTX is taken daily instead of weekly, low-dose MTX is more likely to cause myelosuppression.<sup>6</sup> High-dose MTX related-kidney damage, which can occur due to precipitation of MTX crystals and tubular damage, is very rare with chronic low-dose therapy. In a study of twenty-one RA patients receiving a standard 7.5 mg dose of weekly MTX and concomitant NSAID therapy, no differences in area under the serum concentration versus time curve (AUC), time to maximal MTX concentration (Tmax), or maximal MTX concentration achieved post-dosing (Cmax) were observed over a 2 year period. Creatinine clearance decreased significantly after 6 months of treatment.<sup>26</sup>

When the cases with CKD published in the literature are evaluated, it is seen that after multiple doses or prolonged use of MTX, patients develop bicytopenia or pancytopenia (*Table 1*).<sup>5,23,27-38</sup> However, similar to our cases, pancytopenia has rarely been reported after a single dose of MTX (*Table 2*).<sup>18,40-42</sup> 16 (7 females, 43.8%) of 24 patients with CKD who developed bicytopenia or pancytopenia received multiple MTX doses, while

8 (4 females, 50%) received a single dose of MTX. Median ages [54 (range: 22-68) vs. 60 (range: 21-76) years, respectively], gender distributions and dialysis modalities between single-dose and multiple-dose MTX groups were comparable. One of our patients was stage 3 CKD, 17 out of 24 patients were on maintenance hemodialysis and 6 were on peritoneal dialysis. Depletion of folate prior to the initiation of MTX and the lack of folate supplementation may have contributed to bone marrow toxicity in some patients.<sup>27</sup> If the mean corpuscular volume (MCV) is above 94 fl during MTX treatment, hematological toxicities may be predicted in some patients. Co-administration of MTX with low-dose oral folic acid (5 mg/day) can sometimes reduce the incidence of myelosuppression. However, leukopenia may occur despite folic acid or folinic acid supplements in uremic patients receiving long-term low-dose MTX, and folate supplement may not reduce the risk of hematological toxicity and the possibility of discontinuation of treatment.<sup>28,39</sup> None of those receiving a single dose of MTX received folic acid or calcium folinate supplements before treatment. Only 6 of those receiving multiple doses of MTX received pre-treatment supplement. None of our patients used folic acid before MTX.

In patients with MTX-induced pancytopenia, oral mucositis and fever are the common symptoms at presentation, similar to our cases (*Tables 1 and 2*). These symptoms should alert the clinician to suspect neutropenia. Non-survivor uremic patients with pancytopenia had lower nadir leukocyte counts and higher MTX levels than those of survivors. The highest methotrexate level leads to more severe bone marrow toxicity and the lowest leukocyte count and may worsen the prognosis.<sup>32</sup> The median cumulative MTX dose in multiple-dose MTX group was statistically insignificantly higher than that of single dose MTX group [15 (range: 7.5-100) vs. 7.5 (range: 2.5-25) mg, respectively,  $p=0.053$ ]. However, the cumulative dose of 3 patients was not reported. After developing MTX toxicity, 12 of 24 patients had MTX concentration measured at different times. Different toxicity reference values have been reported in the literature ( $>0.1$ ,  $>0.01$  or  $>0.02$   $\mu\text{mol/L}$ ). In some patients, the MTX concentration was very high (range: 0.06-0.53  $\mu\text{mol/L}$ )<sup>18,31-33,37,38,41</sup>, while in others it was measured normal (0.005  $\mu\text{mol/L}$ )<sup>29</sup> or slightly

high (range: 0.02-0.03  $\mu\text{mol/L}$ ).<sup>34,36,40,42</sup> In our cases, MTX level could not be measured. Really, myelosuppression may become evident in the setting of prolonged elevated serum levels of MTX. Mortality rates of single dose ( $n=3$ , 37.5%) and multiple-dose ( $n=4$ , 25%) MTX groups were similar. The main cause of death in pancytopenic patients with CKD was sepsis and multiple organ failure. In analysis of 25 cases with MTX-induced pancytopenia between 1999 and 2004, the severity of pancytopenia correlated with MTX dose. 32% ( $n=8$ ) of the patients had impaired renal function, and the mortality rate was 28%.<sup>24</sup>

Currently, MTX use is controversial in dialysis patients, even at a low dose. Stage 2 CKD is not associated with increased toxicity.<sup>43</sup> A significant reduction of MTX clearance is observed in patients with stage 3 CKD. However, no prediction for the individual patient is possible due to the wide variation in pharmacokinetics.<sup>44</sup> Peritoneal dialysis, conventional hemodialysis, hemoperfusion and plasmapheresis have been reported to have little effect on the removal of polyglutamated MTX metabolites within cells in MTX intoxication.<sup>5,18,29,45,46</sup> Hemodialysis and hemoperfusion methods can effectively remove approximately 50% of MTX that binds to proteins. However, with a post-dialysis rebound, MTX concentration returns to 90-100% of its level prior to the procedure.<sup>29</sup> While plasma MTX concentrations can be reduced by 26% by plasma exchange or exchange transfusion, hemodiafiltration can decrease its concentrations by 82% over 3 days.<sup>36</sup> Diskin et al<sup>33</sup> reported that the clearance of MTX on peritoneal dialysis was less effective than that on hemodialysis. In contrast, high flux hemodialysis reduced plasma MTX concentrations by 75.5% within 4-12 hours.<sup>47</sup> In another study, serum levels of MTX have been shown to be efficiently reduced by high-flux hemodialysis dialyzers of  $92.1 \pm 10.3$  mL/min.<sup>48</sup> Intensive-cycler peritoneal dialysis and high-flux hemodialysis are potential options for effective removal of MTX.<sup>49</sup> However, the possibility of removing the drug in the case of toxicity may still be limited.<sup>50</sup> We did not change the current dialysis treatment modalities in both of our patients. In the presence of advanced renal failure and dialysis patients, even at low doses, MTX has a higher risk of toxicity due to higher plasma levels and longer half-lives. MTX can be detected even up

**Table 1.** The characteristics of patients with chronic kidney disease (CKD) who developed pancytopenia after single dose methotrexate (MTX)

Ref.	Age, sex	CKD stage (duration) and co-morbidities	MTX Indication	MTX (Dose/duration/cumulative dose)	Folic Acid	Clinical findings	WBC/PNL (cells/ $\mu$ L)	Outcomes
27	49, M	Stage 5-HD, DM, HT	Myositis	IV weekly/2 doses/-	No	pharyngitis, oral mucositis, loose stools, fever, normal platelet	900/330	Improved
27	52, M	Stage 5-HD, DM, HT	Myositis	2.5 mg/wk, IM, then 5 mg/wk/-/-	Yes	pneumonia, sepsis	2,200/-	Improved
27	61, F	Stage 5-HD, DM, HT	Psoriasis, PA	2.5 mg/wk, PO, single dose, stop due to nausea and ~1 month later; 2.5 mg/wk, IM/2 doses/7.5 mg	No	sore throat, fever, sepsis	50/0	Died
30	60, F	Stage 5-HD, DM, HT	RA	5 mg/wk, PO/2 doses/10 mg	No	diarrhea, buccal ulcerations (4 days after 2 <sup>nd</sup> dose)	1,300/66	Improved
5	74, F	Stage 5-HD, amyloidosis	RA	5 mg/wk, PO/two doses/10 mg (interval of 5 days)	No	stomatitis with multiple ulcerations (1 day before 2 <sup>nd</sup> dose), fever	1,700/306	Improved
23	64, M	Stage 5-PD	Psoriasis	-/-/35 mg	No	mouth ulceration, fever, oropharyngeal ulceration, normal platelet, invasive pulmonary aspergillosis after resolution of neutropenia	300/0	Died
33	60, M	Stage 5-PD (14 months), HT, CAD, emphysema	RA	10 mg/wk, SC/2 doses/20 mg	No	nausea, hematemesis, stomatitis, anorexia, odynophagia, septic shock	700(300)/-	Died
28	33, F	Stage 5-PD (5 years), lupus nephritis	Intractable arthritis	5 mg/wk, PO/4 doses/25 mg	Yes	mucositis, tachycardia, general weakness, chest discomfort, respiratory distress, anemic appearance, leg edema	1,500/960, after 5 days 600/90	Improved
34	66, M	Stage 5-HD, HT	psoriasis, PA	5 mg/wk, PO/2 doses/10 mg	Yes	nausea, severe sore throat, low-grade fever, toxic erythrodermia, oral mucositis, buccal ulcerations, liver toxicity, oesophageal candidiasis	-/70	Improved
35	55, F	Stage 5-HD (7 years)	RA	7.5 mg/wk, PO/12 doses/90 mg	Yes	fever, general fatigue, multiple oral ulcers, erythroderma rash with cutaneous ulceration, carbuncles	630/-	Improved
37	76, M	Stage 5-HD (5 years), HT	Bullous pemphigoid	2.5 mg twice weekly, PO/3 doses/7.5 mg	Yes	pneumonia	550/-	Died
32	61, F	Stage 5-PD (6 years)	Intractable chronic eczema	7.5 mg/wk, PO/2 doses/15 mg	No	general malaise, stomatitis, fever, sepsis	30/-	Improved
38	21, F	Stage 5-HD (9 years), hypovolemic shock	Ectopic pregnancy	100 mg, IV	No	fever, sore throat, mouth, pruritis, diffuse maculopapular rash on face and body surface, oral thrush, mucositis, mild trismus	730/20	Improved
31	48, M	Stage 5-HD (5 years)	Bullous pemphigoid	10 mg/wk, PO/2 doses/10 mg	yes	acute shortness of breath, non-productive cough, fever, MTX pneumonitis	1,800/-	Improved
36	46, M	Stage 5-HD (12 years), glomerulonephritis	RA	-	No	epigastric pain, nausea, diarrhea, pneumatosis intestinalis	690/-	Improved
29	68, M	Stage 5-PD (3 years)	Granulomatosis with polyangiitis	7.5 mg, PO/2 doses/15 mg	No	odynophagia, asthenia, adynamia, bleeding from gums, oral ulcers, painful skin lesions, fever, necrotic lesions on the lower lip, ulcers on the cheeks, aphthae on the tongue, erythematous macules, mucosal membranes lesions, septic shock	1,300/182	Improved

WBC: leukocyte, PNL: neutrophil, F: female, M: male, HD: hemodialysis, PD: peritoneal dialysis, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, RA: rheumatoid arthritis, PA: psoriatic arthritis, IV: intravenously, IM: intramuscular, PO: orally, SC: subcutaneously.

**Table 2.** The characteristics of patients with chronic kidney disease (CKD) who developed pancytopenia after single dose methotrexate (MTX)

Ref.	Age, sex	CKD stage (duration) and co-morbidities	MTX indication	MTX dose	Clinical findings	WBC/PNL (cells/ $\mu$ L)	Outcomes
18	52, F	Stage 5-HD	RA	2.5 mg, PO	Fever, pharyngitis, stomatitis-oral ulcerations, rash, bacteremia, a large subdiaphragmatic abscess at autopsy	500/120	Died
18	47, F	Stage 5-HD, scleroderma, Raynaud's phenomenon, renovascular HT	polymyositis	2.5 mg, PO	Fever, pneumonitis, normal platelet	1,500/495	Improved
40	57, M	Stage 5-HD	RA	5 mg, PO	Fever, stomatitis with multiple ulcers, fatigue, sepsis, jaundice	100/-	Improved
41	56, M	Stage 5-HD (7 years), IgA nephropathy, chronic hepatitis C infection	Pustular psoriasis, PA	2.5 mg, PO	Fever, deranged liver function, paroxysmal supraventricular tachycardia, acute coronary syndrome	500/-	Died
42	68, M	Stage 5-PD, HT, nonischemic cardiomyopathy, pulmonary HT, wandering atrial pacemaker, mesenteric atherosclerosis	Refractory squamous cell carcinoma of the hands	25 mg, IL	Nausea, general malaise, shortness of breath, pustular hand lesions, mucositis, deranged liver function, fever	1,300(600)/-	Improved
*	58, F	Stage 3	RA	12.5 mg, PO	Abdominal pain, chest discomfort, vomiting, skin rash	1,200/160	Improved
*	43, M	Stage 5-HD (3 months)	Psoriasis, PA	12.5 mg, PO	Diarrhea, anorexia, chills, fever, sepsis, mucositis, hepatotoxicity	3,100/590	Died
*	22, F	Stage 5-HD (13 years)	Psoriasis	10 mg, IM	Fever, vomiting, nausea, diarrhea, epistaxis, stomatitis, sepsis	1,810/390	Improved

\* present cases, WBC: leukocyte, PNL: neutrophil, F: female, M: male, HD: hemodialysis, PD: peritoneal dialysis, HT: hypertension, RA: rheumatoid arthritis, PA: psoriatic arthritis, PO: orally, IM: intramuscular, IL: intralesional.

to 3 weeks after taking small doses of 2.5 mg.<sup>29</sup> Therefore, it may not be appropriate to administer MTX therapy in patients with stage 4 and stage 5 CKD.

## Conclusion

In our patients with renal dysfunction, MTX-induced pancytopenia developed within a few days after a single dose of MTX administration. Since the mechanisms of action and dose-response relationships are not fully elucidated, there is considerable heterogeneity in RA therapy with low dose MTX.<sup>3</sup> Recently, the 2016 update of European League Against Rheumatism recommendations for the management of RA suggests administering oral or subcutaneous MTX with short-term glucocorticoid initially, if tolerated, rapidly increasing the dose to 25-30 mg per week and evaluating the response to treatment within 8-12 weeks.<sup>51</sup> In patients with normal renal function, the recommended doses are within a range of 5 to 7.5 mg per week. This dose can be increased by steps of 2.5 to 5 mg, up to a maximal dose of 15 mg/week. However, in patients with renal dysfunction, if necessary, the initial weekly dose should be 2.5 mg, and the dose should be gradually increased by 2.5 mg per week by close monitoring of whole blood count. The maximal dose should not exceed 5-7.5 mg. Some nephrologists recommend applying 30% of the routine dosage.<sup>52</sup> The American College of Rheumatology (ACR) recommend that a routine complete blood count should be performed every

four weeks during the first three months of therapy, every 8 to 12 weeks from three to six months, and every 8 to 12 weeks thereafter, depending upon the nature and/or severity of abnormalities noted during monitoring.<sup>53</sup> Folic acid (1 mg/day) or folinic acid (2.5 mg/week) supplement may be beneficial in all patients receiving MTX, especially those with MCV >100 fl. These low doses does not interfere with the beneficial effects of MTX.<sup>35</sup> If bone marrow toxicity is suspected, MTX treatment should be terminated immediately and the patient's clinical findings should be closely monitored. In fact, if the estimated creatinine clearance is below 30 mL/min, it would be more appropriate to prefer alternative treatments due to the risk of life-threatening myelosuppression.

## Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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