

Pralatrexate-Induced Toxic Epidermal Necrolysis

Esra T. DEMIRSOY¹, Pinar TARKUN¹, Ozgur MEHTAP¹, Elif B. ATESOGLU¹, Ayfer GEDUK¹,
Evren O. DEMIRSOY², Abdullah HACIHANEFIOGLU¹

¹ Kocaeli University Faculty of Medicine, Department of Hematology

² Kocaeli University Faculty of Medicine, Department of Dermatology, Kocaeli, TURKEY

Dear editor,

Toxic epidermal necrolysis (TEN) is a serious, typically drug-induced mucocutaneous disease that is characterized by widespread sloughing of the skin and mucosal membranes.¹ Pralatrexate is a novel synthetic selective antifolate agent. In September of 2009, the Food and Drug Administration approved a novel antifolate drug, pralatrexate for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL).² Pralatrexate was investigated on the treatment of relapsed or refractory other T-cell lymphomas including angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, transformed mycosis fungoides.³

Besides that it can be also observed that skin toxicities including rash, ulceration and skin exfoliation parallel to other antifolate drugs. The 45-year-old woman was diagnosed 4 years earlier with stage 3B PTCL-NOS in 2011. She was received six courses of CHOP chemotherapy. She was attained a complete remission. She was relapsed after one year. She was received two cycles salvage ICE chemotherapy, then she was underwent high-dose chemotherapy with hematopoietic stem-cell transplantation in 2013. She was relapsed for the second time in 2015. She was given two cycles of ICE chemotherapy and after that she was evaluated as stable disease. She was received pralatrexate the dose 30 mg/m² once weekly for 6 weeks in 7-week cycles. She was given vitamin B₁₂ 1 mg intramuscularly every 8-10 weeks

and folic acid 5 mg orally on a daily basis prior to initiating pralatrexate due to guideline recommendations.

The side effects were evaluated according to The NCI Common Terminology Criteria for Adverse Events version 4.0. After receiving first cycle, she was detected grade 3 neutropenia, thrombocytopenia and grade 2 mucositis. She was received the second dose of pralatrexate as 20 mg/m² to manage adverse drug reactions.

She developed severe hemorrhagic bullous lesions and grade 3 mucositis on her mouth, ocular and genital mucosa two days later, she had received the second dose of pralatrexate. In additionally, she developed a painful, tender erythematous maculopapular rash with a dark center involving firstly on the upper torso which progressed into large bullae. Then, they spread rapidly in a caudal direction to involve her entire body (affecting more than 60% of total body surface area) within 2 days. The Nikolsky's sign was positive. Within two days, these lesions evolved, progressing to extensive desquamation of most of the patient's body surface area (Figure 1).

She developed grade 4 anemia, thrombocytopenia and neutropenia. She was diagnosed toxic epidermal necrolysis due to pralatrexate. IVIG 0.5 g/kg per day for four days long was received on the 2nd day after the onset of the disease.



Figure 1. Extensive desquamation on the torso and the arm

Additionally, the standard symptomatic management included pain control with opioid analgesics, prevention of stress ulcers, nutrition and fluid support. Topical wounds care was treated with mupirocin and 0.9% NaCl four times a day. Granulocyte colony stimulating factor was started due to neutropenia. She had a fever during this period, she was started piperacillin-tasobactam and teicoplanin. She remained neutropenic. She died six days after receiving second dose of pralateraxate because of sepsis and multiple organ failure.

TEN is an acute life-threatening mucocutaneous disease that involves epidermal sloughing of >30% of the body surface area. Drugs are responsible for 80-95% of TEN cases. The pathophysiology of TEN is not fully understood. TEN is a T-cell mediated reactions with CD8+ cells acting which is a paradigm of delayed hypersensitivity reaction. It is considered as drugs trigger hapten or directly cytotoxic cellular immunity and this causes activation of cellular immune system against keratinocytes in the epidermis.¹

SCORTEN is an seven parametered index which is developed for TEN in order to predict the severity of disease and risk of mortality. One point is given for each of the following factors: 1) age > 40 years 2) malignancy 3) serum bicarbonate < 20 mmol/L 4) heart rate > 120/minute 5) serum glucose > 252 mg/dl 6) epidermal detachment > 10% of body surface area 7) serum blood urea nitrogen >28 mg/dl.⁴ The mortality rate of TEN is approximately 25% to 30%. The mortality risk increases according to SCORTEN score. Mortality rate is 90% for those with ≥ 5 points in SCORTEN parametres.⁵

It has recommended that SCORTEN score has been evaluated on day 1and day 3 in hospitalization for TEN diagnosed patient.⁶

In our case , SCORTEN score for day 1 was graded four and it was graded six for day 3. In additionally, we observed a serious grade 4 myelosuppression due to pralatrexate.

Antifolate drugs cause, focal or widespread epidermal necrosis.the skin reaction is high probably

owing to a direct massive cytotoxic effect against endothelial cells.⁷ In addition to this TEN cases related to antifolate drugs two mechanisms can play role in pathobiology. One of the two mechanism is direct endothelial toxicity and the other is hypersensitivity reaction.^{7,8}

In PROPEL study, the most common side effects were mucositis, nausea, thrombocytopenia, and fatigue. The most common grade 3 or 4 side effects were thrombocytopenia, mucositis, neutropenia, and anemia. Mucositis was the most common reason for dose regulation. While the subgroup of skin toxicity has rash (15%) and pruritis (14%) was detected. On the contrary grade 4 skin toxicity was not appointed.³ In an other study on receiving the different dosage of pralatrexate, the skin toxicities (21-23%) that have all grades were reported. Most of the skin toxicities were reported as grade 1-2, but grade 4 skin toxicity was not reported.⁹ In both studies, there were no data about TEN which is a side effect related to pralatrexate. In our case, the patient presented an extensive skin necrolysis and a serious bone marrow suppression occurring after pralatrexate administration. Leucovorin rescue is not recommended as a routine treatment of pralatrexate. Koch, et al. were reported that using leucovorin preemptively in cutaneous T-cell Lymphoma patients 24 hours following administration of pralatrexate, causes a significant decrease on side effects.¹⁰

In conclusion, skin toxicity and TEN cases were reported during the use of antifolate drugs especially as methotrexate. Pralatrexate is a new generation antifolate drug that it can be observed skin toxicity as a group toxicity. Herein this case we would like to increase awareness of this potential life-threatening complications like TEN. If we can determine the potential patients who have serious side effects developing during pralatrexate treatment, we can decrease side effects when we treat the patient with preemptive leucovorin rescue from the beginning.

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Correspondence:

Dr. Esra Terzi DEMIRSOY
Kocaeli Üniversitesi Tip Fakültesi
Hematoloji Anabilim Dalı
41380 Umuttepe, KOCAELİ, TURKEY

Tel/Fax: (+90-262) 303 80 03
e-mail: esraterzi@gmail.com