Research Article / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2023; 62 (2): 266-271

Pralatrexate in patients with relapsed and refractory T-cell lymphomas: real world data

Relaps ve refrakter T-hücreli lenfoma hastalarında pralatrexate kullanımı: gerçek yaşam verileri

Eren Arslan Davulcu[1] Fatma Keklik Karadağ[2] Ayşenur Arslan[3] Zühal Demirci[4]
Derya Demir[5] Nur Soyer[4] Fahri Şahin[4] Güray Saydam[4]

[1] University of Health Sciences Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Hematology Clinic, Istanbul, Türkiye

[2] University of Health Sciences Tepecik Training and Research Hospital, Hematology Clinic, Izmir, Türkiye

[3] Osmaniye Public Hospital, Osmaniye, Türkiye

[4] Ege University Faculty of Medicine, Hematology Department, İzmir, Türkiye

[5] Ege University Faculty of Medicine, Pathology Department, İzmir, Türkiye

ABSTRACT

Aim: T-cell lymphomas are a subtype of Non-Hodgkin lymphoma with a poor prognosis and treatment options are limited. Pralatrexate, an antimetabolite drug, has been approved for the treatment of relapsed and refractory T-cell lymphoma.

Materials and Methods: Our study retrospectively evaluated relapsed and refractory T-cell lymphoma patients who received pralatrexate in terms of efficacy and safety of the drug.

Results: A total of 13 patients were recruited. The median age at diagnosis was 63 years. The most common histologic types were *mycosis fungoides* with large cell transformation (31%) and angioimmunoblastic T-cell lymphoma (31%). The median number of prior systemic therapies before pralatrexate was 2 (range 1-6). The most common side effect was mucositis (54%). The overall response rate was 38% (15% complete remission and 23% partial remission). The median OS was 32±6.5 months and PFS was 6.78±1.6 months.

Conclusion: Our study provided real-world data on the efficacy and safety of pralatrexate and supports current literature. This drug has acceptable toxicity and significant effectiveness on peripheral T-cell lymphomas.

Keywords: T-cell lymphoma, lymphoma, pralatrexate.

ÖZ

Amaç: *T-hücreli lenfomalar, non-Hodgkin lenfomaların kötü prognozlu bir alt tipidir ve tedavi seçenekleri sınırlıdır. Bir antimetabolit ilaç olan pralatrexate, relaps ve refrakter T-hücreli lenfoma tedavisinde onaylanmıştır.*

Gereç ve Yöntem: *Çalışmamızda pralatreksat alan relaps ve refrakter T-hücreli lenfoma hastaları ilacın etkinlik ve güvenliliği açısından retrospektif olarak değerlendirilmiştir.*

Bulgular: *Toplam 13 hasta alındı. Tanı anındaki ortanca yaş 63 olarak bulundu. En yaygın histolojik tipler, büyük hücre transformasyonu gösteren mikozis fungoides (%31) ve anjiyoimmünoblastik T-hücreli lenfomaydı (%31). Pralatreksattan önceki medyan sistemik tedavi sayısı 2'ydi (1-6 aralığında). En sık görülen yan etki mukozitti (%54). Genel yanıt oranı %38'di (%15 tam remisyon ve %23 kısmi remisyon). Ortanca OS 32±6,5 ay ve PFS 6,78±1,6 aydı.*

Corresponding author: Eren Arslan Davulcu
University of Health Sciences Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Hematology Clinic, Istanbul, Türkiye
E-mail: *erenarslan85@yahoo.com*
Application date: 25.12.2022 Accepted: 21.01.2023

Sonuç: *Çalışmamız, pralatreksatın etkinliği ve güvenliği hakkında gerçek dünya verileri sağlamıştır ve sonuçlar mevcut literatürü desteklemektedir. Toksisitesi kabul edilebilir düzeydedir ve periferik T-hücreli lenfomalar üzerinde önemli etkinliği vardır.*

Anahtar Sözcükler: *T-hücreli lenfoma, lenfoma, paralatrexate.*

INTRODUCTION

T-cell lymphomas (TCL) are mature T and natural killer (NK) cell neoplasms which is a group of non-Hodgkin lymphomas (NHL) (1). Among peripheral TCL (PTCL) the most common subtypes are angioimmunoblastic T-cell lymphoma (AITCL), systemic anaplastic large cell lymphoma (sALCL), and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Cutaneous TCL (CTCL) consists of a heterogeneous group of diseases, some of which are indolent, while there are aggressive types that require systemic chemotherapy. The most common subtypes are mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) (1, 2). Despite advances in NHL treatment, TCL has a poor prognosis (2). In general, the most frequently applied regimens are cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and CHOP+etoposide (CHOEP), but treatment responses are heterogeneous and less than satisfactory (2, 3). In recent years, combining brentuximab vedotin with chemotherapy (breantuximab+CHP) for CD30-positive PTCL showed superior results compared to classical chemotherapy (CHOP) in the first line (4). Consolidation with autologous stem cell transplant in the front-line setting is also recommended (2). In relapsed-refractory patients, there are options with comparable outcomes (5).

Pralatrexate is an anti-folate agent which is highly selective for reduced folate carrier-1, which is a protein highly expressed in malign T-cells. Pralatrexate has been shown to be superior to other antimetabolites, including methotrexate, in preclinical studies (6-8). A multicenter phase 2 PROPEL study evaluated the efficacy and tolerability of pralatrexate, and showed an overall response rate (ORR) of 29%, a median overall survival (OS) of 14.5 months, and a median progression-free survival (PFS) of 3.5 months in relapsed and refractory PTCL (9). Thus, pralatrexate was approved by the US Food and Drug Administration as a single agent in relapsed and refractory PTCL (10).

Our study is designed to retrospectively evaluate relapsed and refractory patients with TCL who received pralatrexate in terms of efficacy and safety of the drug.

MATERIALS and METHODS

We retrospectively evaluated TCL patients who received pralatrexate because of relapsed and refractory disease. Patients older than 18 years were available for inclusion.

Pralatrexate was administered intravenously in a 7-week cycle at the dose of 30 mg/m^2/week for 6 weeks, following 1 week of rest. All patients received parenteral vitamin B12 and oral folic acid supplementations in order to reduce mucositis. Pralatrexate treatment continued until the progression or occurrence of severe adverse side effects.

We obtained data regarding their age at diagnosis, gender, histopathology, stage of the disease at the time of diagnosis, type of and the median number of prior systemic treatments, median number of pralatrexate cycles, best response, progression, death, and toxicities. Topical therapies, localized radiotherapy, and oral steroids were not classified as prior systemic therapies. Evaluation criteria for treatment response were based on IWC (11). Physical examination, complete blood count, basic biochemical tests, and, where necessary, bone marrow biopsy and PET CT were performed on each patient for staging or evaluation of treatment response. Toxicity was evaluated in every visit by physical and laboratory examinations, adverse events were graded using National Cancer Institute Common Toxicity Criteria for Adverse Events scale, version 3.0.

Outcome measures were ORR, PFS, OS, and toxicity. Data were reported as frequency (percentage) or median for categorical and continuous variables. Survival analyses were performed using the Kaplan–Meier method. PFS and OS were calculated from the start of therapy until disease progression or death, or until the last follow-up. IBM SPSS Statistics 25 for Windows was used for statistical analyses.

This study was approved by the local ethics committee and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

RESULTS

A total of 13 relapsed and refractory TLC patients received pralatrexate in our center. The baseline characteristics of patients are detailed in Table-1.

The median number of prior systemic therapies before pralatrexate was 2 (range 1-6). The median number of pralatrexate cycle numbers was 5 (range 1-34).

The best response to pralatrexate was complete remission (CR) in 2 patients (15%), partial response (PR) in 3 patients (23%), progressive disease (PD) in 8 patients (62%), and resulting in an ORR of 38%. Median OS was 32±6.5 months and PFS was 6.78±1.6 months respectively (Figure-1 and Figure-2). Adverse events are summarized in Table-2. For the patient who developed hepatitis B reactivation, the drug had to be interrupted for 2 months. This patient is still taking pralatrexate and is being followed up with a CR. Dose modification was required in three patients who developed grade 3-4 mucositis and hematological side effects. No drug-induced anemia developed in our patient group. The treatment details of patients are summarized in Table-3.

Table-1. Patients' characteristics.

Parameter	Number	Percentage (%)
Gender		
-Male	7	54
-Female	6	46
Median age at diagnosis	63 years (Range 40-71 years)	
Histopathology		
-MF LCT	4	31
-AITCL	4	31
-PTCL, NOS	3	23
-sALCL-ALK negative	2	15
Type of prior systemic therapies		
-IFN	4	30
-Electron beam	1	8
-Bexaroten	1	8
-CHOP/CHOP like therapy	8	62
- Non-platinum-containing multi-agent chemotherapy	3	23
- Platinum-containing multi-agent chemotherapy	7	54
-PUVA	3	23
-Brentuximab vedotin	3	23
-Tretinoin	1	8
-Autologus stem cell transplantation	3	23

MF LCT: *Mycosis fungoides* with large cell transformation, PTCL, NOS: Peripheral T-cell lymphoma, not otherwise specified, AITCL: Angioimmunoblastic T-cell lymphoma, sALCL-ALK negative: Systemic anaplastic large cell lymphoma, ALK-negative, IFN: Interferon, CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone, PUVA: Psoralen ultraviolet A

Table-2. Adverse events.

	All grades (Grade 1-4) Number (%)	Grade 3-4 Number (%)
Mucositis	7 (54%)	3 (23%)
Thrombocytopenia	2 (15%)	1 (8%)
Neutropenia	2 (15%)	2 (15%)
Hepatitis B virus infection	1 (8%)	

Table-3. Treatment details of patients.

Patient No	Histopathology	Stage	1st line treatment	2nd line treatment	3rd line treatment	4th line treatment	5th line treatment	6th line	Best response to pralatrexate	Status
1	MF LCT	4	IFN+electron BEAM+bexaroten	CHOEP	Methotrexate	Pralatrexate	Brentuximab	-	PR	PD, exitus
2	AITCL	3	CHOEP	GEMOX	Pralatrexate	Bendamustine	-	-	PR	PD, exitus
3	sALCL-ALK negative	3	EPOCH	Autologus SCT	GIFOX	Brentuximab	Paralatrexate	-	CR	CR, alive
4	AITCL	4	CHOP	Brentuximab	Pralatrexate	ICE	-	-	PD	SD, alive
5	MF LCT	2	IFN+PUVA	EPOCH	Pralatrexate	-	-	-	PD	PD, exitus
6	PTCL, NOS	3	Brentuximab	Pralatrexate	ICE	Autologus SCT		-	PD	PD, exitus
7	AITCL	3	CHOP	Pralatrexate	-	-	-	-	PD	PD, Exitus
8	AITCL	4	CHOEP	ICE	Autologus SCT	Pralatrexate	Lenalidomide	-	PD	SD, Exitus
9	MF LCT	4	IFN+PUVA	Pralatrexate	Bendamustine	-	-	-	PD	PD, exitus
10	PTCL, NOS	3	CHOEP	GEMOX	Pralatrexate	-	-	-	PD	PD, exitus
11	Salcl-ALK negative	1E	CHOEP	Pralatrexate	-	-	-	-	CR	CR, alive
12	MF LCT	2B	IFN+PUVA+tretinoin	Pralatrexate	-	-	-	-	PD	PD, exitus
13	PTCL, NOS	4	CHOP	ESHAP	Autologus SCT	Pralatrexate	Romdepsine	Belinostate	PR	PD, exitus

MF LCT: Mycosis fungoides with large cell transformation, PTCL, NOS: Peripheral T cell lymphoma, not otherwise specified, AITCL: Angioimmunoblastic T cell lymphoma, sALCL-ALK negative: Systemic anaplastic large cell lymphoma, ALK negative IFN: Interferon, CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone, EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone, PUVA: Psoralen+ ultraviolet A, GEMOX: Gemcitabine, oxaliplatin, ICE: Ifosfamide, carboplatin, etoposide, ESHAP: Etoposide, methylprednisolone, cisplatin, cytarabine, GIFOX: Gemcitabine, ifosfamide, oxaliplatin, HCT: Hematopoietic stem cell transplantation, PD: Progressive disease, CR: Complete remission, SD: Stable disease, PR: Partial response.

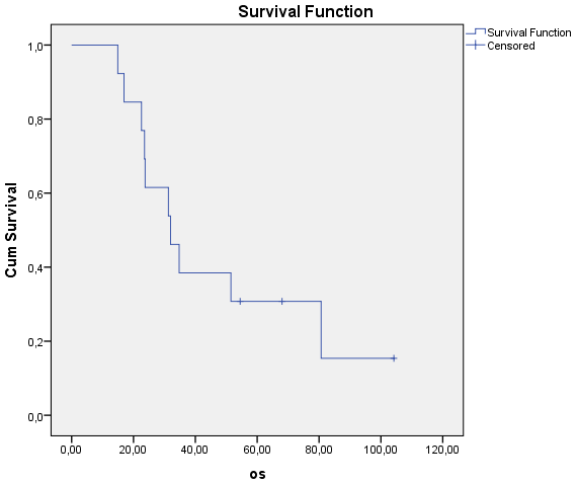

Figure-1. Overall survival.

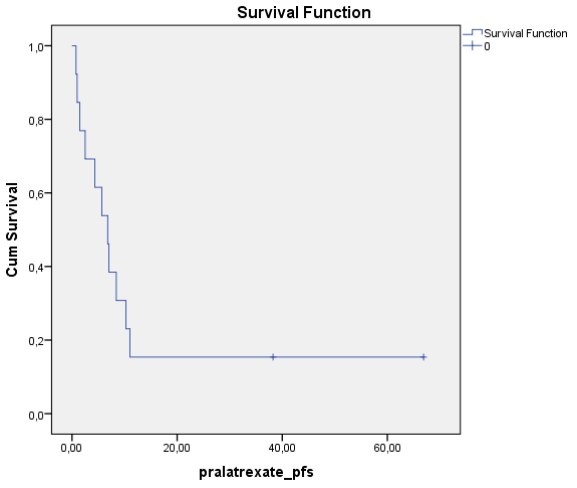

Figure-2. Progression free survival.

DISCUSSION

Patient demographics are quite similar between studies on pralatrexate treatment in TCL patients. The median age was 63 years in our patient cohort, compared with 69 years in the Australian study (12), 71 years in the Korean study (13), and 58 years in the PROPEL study (9). In all other studies, the most common histological type was PTCL NOS, while in our group it was mycosis fungoides with large cell transformation (MF LCT) and AITCL. The reason for the difference in distribution may be that our patient group included relatively few patients.

TCL patients are usually those who are in the advanced stage and have received multiple lines of therapy. In our study, patients received pralatrexate as their ≥3rd line therapy of 62% (8 patients). The ORR rate (38%) and CR rate (15%) in our study were similar to the rates of ORR and CR of 35.5%- 13% (12), 29%-11% (9), and 21.1%- 7.9% (13) respectively, in other studies.

Pralatrexate also acts as a bridge in the transition period before allogeneic stem cell transplantation in TCL patients. However, in our patient group, there was no patient who had allogeneic stem cell transplantation due to the development of mortality or insufficient bridging function, even though it was planned.

The toxicity profile encountered by the patients in our study was similar to other pralatrexate studies. To our knowledge, the only patient in our study who reported hepatitis B virus infection while taking pralatrexate. Before treatment, it was known that he was negative for hepatitis B surface antigen and anti-HBS antibody. It was thought that it may have been caused by reactivation or a new infection. He still continues to use pralatrexate under antiviral therapy after a 2-month break from pralatrexate.

In our study, 2 patients were still receiving pralatrexate with complete response (one was on the 32nd cycle and the other was on the 34th cycle at the end of the study period). The histological type of both patients was systemic anaplastic large cell lymphoma, ALK-negative. Our study did not have a sufficient number of patients to evaluate histological interspecies treatment responses. There is no information about this yet in other publications in the literature.

Our study has many limitations. The small number of patients, the heterogeneity of the distribution of histological types, the lack of a fixed approach in the choice of treatment, and the order of initiation of pralatrexate are the most important reasons.

CONCLUSION

Our research is important in providing real-world data on the efficacy and safety of pralatrexate, and our results support literature data on these issues. In such a poor prognosis group, pralatrexate also supports that it is an effective and safe treatment method.

Conflict of interest: The authors declare that they do not have any conflict of interest. This research did not receive any funding.

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
2. Moskowitz AJ, Lunning MA, Horwitz SM. How I treat the peripheral T-cell lymphomas. Blood 2014;123:2636-44.
3. Abouyabis AN, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A Systematic Review and Meta-Analysis of Front-line Anthracycline-Based Chemotherapy Regimens for Peripheral T-Cell Lymphoma. ISRN Hematol 2011;2011:623924.
4. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2019;393:229-240.
5. Petrich AM, Rosen ST. Peripheral T-cell lymphoma: new therapeutic strategies. Oncology (Williston Park) 2013;27:878-84.
6. Toner LE, Vrhovac R, Smith EA, et al. The schedule-dependent effects of the novel antifolate pralatrexate and gemcitabine are superior to methotrexate and cytarabine in models of human non-Hodgkin's lymphoma. Clin Cancer Res 2006;12:924-32.
7. Wang ES, O'Connor O, She Y, Zelenetz AD, Sirotnak FM, Moore MA. Activity of a novel anti-folate (PDX, 10-propargyl 10-deazaaminopterin) against human lymphoma is superior to methotrexate and correlates with tumor RFC-1 gene expression. Leuk Lymphoma 2003;44:1027-35.
8. Marchi E, Paoluzzi L, Scotto L, et al. Pralatrexate is synergistic with the proteasome inhibitor bortezomib in in vitro and in vivo models of T-cell lymphoid malignancies. Clin Cancer Res 2010;16:3648-58.
9. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 2011;29:1182-9.
10. Malik SM, Liu K, Qiang X, et al. Folotyn (pralatrexate injection) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma: U.S. Food and Drug Administration drug approval summary. Clin Cancer Res 2010;16:4921-7.
11. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.
12. Bhurani M, Admojo L, Van Der Weyden C, et al. Pralatrexate in relapsed/refractory T-cell lymphoma: a retrospective multicenter study. Leuk Lymphoma 2021;62:330-6.
13. Hong JY, Yoon DH, Yoon SE, et al. Pralatrexate in patients with recurrent or refractory peripheral T-cell lymphomas: a multicenter retrospective analysis. Sci Rep 2019;9(1):20302.