TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

The Outcome in Patients With Peripheral T-Cell Lymphoma Treated With Pralatrexate: A Single-Centre Experience

Aydan AKDENIZ[1], Nurcan YILMAZ CETIN[2], Mahmut Bakir KOYUNCU[3], Gulhan OREKICI[4], Pelin AYTAN[1], Anil TOMBAK[1]

[1]Division of Hematology, Department of Internal Medicine, Mersin University Hospital, Mersin, Turkey
[2]Department of Internal Medicine, Mersin University Hospital, Mersin, Turkey
[3]Department of Hematology, Adana City Hospital, Adana, Turkey
[4]Department of Statistics, Mersin University Hospital, Mersin, Turkey

ABSTRACT

Background Peripheral T-cell lymphoma (PTCL) accounts for 10-15% of all non-Hodgkin lymphomas. Five-year overall survival is very poor in all subtypes except in ALK positive anaplastic large cell lymphomas (ALCL). Patients in relapsed-refractory (RR) setting, treatment options are very limited, particularly in patients with poor performance or advanced age. Pralatrexate has been shown to improve remission and survival rates in RR PTCL. We aimed to evaluate the response rates, efficacy and adverse event profile of pralatrexate used in RR PTCL in our center.

Material and Methods Patients followed in hematology department of Mersin University with the diagnosis of RRPTCL and treated with pralatrexate were included in study. Their demographical and clinical data were documented. Response to treatment with pralatrexate was evaluated.

Results Median follow up time was 14 months and mean age at diagnosis was 50.6 (±17.9) in totally 11 patients. Patients received median 2 cycles of pralatrexate. Six patients were refractory to treatment while 5 patients achieved at least partial remission.

Conclusions PTCL has the worst prognosis among all types of lymphomas. Cure rates are still low and new therapeutic options are needed.

Turk J Int Med 2022;4(1):20-24
DOI: 10.46310/tjim.984313

Keywords: *Non-Hodgkin lymphoma, peripheral T-cell lymphoma, pralatrexate.*

Received: August 18, 2021; Accepted: December 19, 2021; Published Online: January 29, 2022

Address for Correspondence:
Aydan Akdeniz, MD
Division of Hematology, Department of Internal Medicine,
Mersin University Hospital, Mersin, Turkey
E-mail: akdenizdr@hotmail.com

Introduction

Peripheral T-cell lymphoma (PTCL) accounts for 10-15% of all non-Hodgkin lymphomas (NHL). PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T cell lymphoma (AITL), NK/T cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell lymphoma (ALCL, ALK+, ALK-) are the most common subtypes.[1] Five-year overall survival is 70-79% in ALK+ ALCL, while it is quite poor in other subtypes (14% to 35%). Similar to B-cell lymphomas, anthracycline-based chemotherapies such as cyclophosphamide, doxorubicin, vincristine and prednisolone, etoposide (CHOP/CHOEP) or cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyperCVAD) are used in front-line treatment. Stem cell transplantation (SCT) should be planned as consolidation procedure after high-dose chemotherapy in patients who achieved remission and are eligible.[2] Allogenic SCT should be considered in patients in relapsed or refractory (RR) setting. In CD30-positive PTCL, brentuximab vedotin have been approved based on the randomized ECHELON-2 clinical trial.[3] In patients who are resistant or intolerant to first-line therapy or who have relapsed disease; alemtuzumab, bortezomib, gemcitabine, histone deacetylase inhibitors (romidepsin, belinostat), pralatrexate, monoclonal antibodies (brentuximab, mogamulizumab) are among the new treatment options.[4] Pralatrexate, a dihydrofolate reductase inhibitor, has been shown to improve remission and survival rates in PTCL patients both in early clinical studies and in the PROPEL study and got FDA approval in 2009, and its benefit has been proven by subsequent studies.[5-7] In our study, we aimed to evaluate the response rates, efficacy and adverse event profile of pralatrexate in patients with RR-PTCL in our center.

Material and Methods

Data of patients followed in hematology department of Mersin University Hospital between 1 January 2017 and 1 January 2021 with the diagnosis of PTCL were retrospectively analyzed. Patients treated with pralatrexate with this diagnosis were included in the study. The demographical data of the patients, pathological subtypes, follow-up periods, the number of cycles of pralatrexate they were treated, the number of chemotherapy lines before pralatrexate, side effects and reasons of death were documented. Response assessment was performed with positron emission tomography-computerized tomography (PET-CT) after 2 cycles of treatment. The proportion of patients with at least partial response was defined as overall response rate (ORR). Patients that responders and non-responders were compared in terms of demographics, age at diagnosis, follow-up time, stage, pathological subtypes, number of prior chemotherapy lines and cause of death. The data obtained were evaluated and compared with literature.

Shapiro-Wilk test was used for normality control of continuous variables. Standard deviation values were given for normally distributed variables, min-max and median values were given for non-conforming variables.

Results

Data of a total of 11 patients were accessed. Mean age at diagnosis, median follow-up time, median number of lines of treatment prior to pralatrexate, median number of cycles of pralatrexate, distribution of gender, histopathological subtypes and stage of patients are summarized in Table 1. Prior to pralatrexate, 8 patients received 2 lines and the others received 3 lines of treatment. First-line treatment was CHOP (cyclophosphamide, vincristine, cyclophosphamide, dexamethasone) in 8 patients, EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in 2 patients and dose adjusted EPOCH in 1 patient. No patient had stem cell transplantation prior to pralatrexate. Patients were treated with a median of 2 cycles of pralatrexate. ORR was 45% (4 patients; complete remission [CR], and 1 patient; partial remission [PR]). Two of 5 responder patients were relapsed. One of them was not eligible for SCT, and relapsed in fourth month of pralatrexate treatment, and the other relapsed with central nervous system involvement during the preparation for autologous SCT and has died. Patients treated with combination of pralatrexate and romidepsin were

Table 1. The characteristics of 11 patients.

Parameters	Values
Mean age at diagnosis (years) (mean±SD)	50.6±17.9
Male/Female	8/3
Median follow-up time (month) (min-max)	14 (8-40)
Pathological subtype, n (%)	
PTCL, NOS	5 (45)
ALCL (ALK+)	3 (27)
ALCL (ALK-)	1 (9)
AITL	2 (18)
Median stage (min-max)	4 (3-4)
Pralatrexate, n (%)	
Monotherapy	8 (72)
Combination with romidepsin	3 (27)
Number of patients who have died, n (%)	5 (45)
Median number of lines of treatment prior to pralatrexate (min-max)	4 (2-6)
Median follow-up time after relaps or progression (month) (min-max)	7 (3-25)
Median number of cycle of pralatrexate (min-max)	2 (1-6)
Overall response rate (%)	45

all refractory. As hematological adverse event: moderate neutropenia was seen in 5 of patients. One patient suffered from delayed wound healing. Patient who achieved PR died due to severe heart failure (ejection fraction; 20%) that occurred during the treatment. The mean age of the patients who were died was 68.6. In all three patients who were assessed, CD30 were positive. The responder and non-responder patients are compared in terms of mean age at diagnosis, gender, median follow up times, patological subtypes, stage, cause of death in Table 2.

Discussion

Based on reports presenting real life data, it is clear that RR-PTCL has quite poor outcome among the other RR-NHLs, In a study, 153 patients with RR-PTCL reported to have 5.5 months median overall survival, while it was 2.5 months in another report.[8,9] Although survival cannot be mentioned due to the small number of patients and the short follow-up period, relapsing rates and proportion of primary refractory patients in our study supports the information that the disease has poor prognosis.

Indeed, it is not exactly true to compare results of a clinical trail with large population with a real life data of a limited population. However we aimed to evaluate whether our results supported those in clinical trial. While the overall response rate was 29% in the PROPEL study, which accelerate the approval, it was 45% in our study.6 This supports the promising results of pralatrexate treatment in other studies.[10,11]

When the characteristics of the patients with or without response were compared, it was observed that 80% of patients with PTCL-NOS were refractory to pralatrexate treatment, this result is consistent with literature which mentioned that NOS subtype has worse prognosis.[2] Non-responder patients were younger than responder patients. Although Amengual *et al.*[12] reported better response rates with pralatrexate-romidepsin combination in a phase-1 study, none of the patients, treated with this combination responded in this study. Undoubtedly phase II, III study and real life data will yield more definitive and realistic

Table 1. Characteristics of responding and non-responding patients.

	Responders to pralatrexate (n=5)	Non-responders to pralatrexate (n=6)
Mean age at diagnosis (years) (mean±SD)	56.2±15.4	46±19.8
Male/Female (%)	60/40	84/16
Median follow-up time (month) (min-max)	22 (12-35)	12 (8-40)
Pathological subtype, n (%)		
PTCL, NOS		
ALCL (ALK+)	1 (20)	4 (66)
ALCL (ALK-)	3 (60)	1 (16)
AITL	1 (20)	1 (16)
Stage		
3	1	2
4	4	4
Primary refractory	4	2
Relapsed	1	4
Pralatrexate, n (%)		
Monotherapy	5 (100)	3 (50)
Combination with romidepsin		3 (50)
Number of patients who have died, n (%)	2 (40)	3 (50)
Cause of death	Progression after remission (n=1) Heart failure (n=1)	Progression (n=3)

results. On the other hand, the other combinations with bortezomib and gemcitabine are still under investigation and show promising.[13,14]

Mucositis is the most common adverse event in literature, but it is not detected in our patients so often.[15] All patients were received prophylaxis for mucositis, but we doubted about lack of documentation of side effects in our clinic during the treatment periods. As the most common hematological adverse event inconsistent with the multicenter study of Hong *et al.*[16], not thrombocytopenia but moderate neutropenia was seen in 5 of patients. While edema and tachycardia are the most common cardiac complications in literatüre, one of our patients who had no cardiac pathology except for left ventricular hypertrophy due to hypertension previously, got severe heart failure with treatment and died due to it.[10]

Limitations of the study includes small population of patients, shortness of follow-up duration, lack of assessment of CD30 marker in other 8 patients and lack of genetic assessment (such as mutations of TET2, IDH2, DNMT3A). Lack of documentation of adverse events is also the other limitation.

Conclusions

RR-PTCL has poor prognosis and there are few treatment options. Among these, pralatrexate has a proven efficacy. Despite all the positive and promising results, large population studies with long follow-up duration are needed and new mono and combined therapy modalities should be worked on.

Conflict of interest

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception: AA; Study Design: AA; Supervision: MBK; Data Collection and/or Processing: PA; Materials: NYC Statistical Analysis and/or Data Interpretation: PA; Literature Review: AA, PA; Manuscript Preparation: BY; and Critical Review: AT; Statistics: GO.

References

1. Bhurani M, Admojo L, Van Der Weyden C, Twigger R, Bazargan A, Quach H, Zimet A, Coyle L, Lindsay J, Radeski D, Hawkes E, Kennedy G, Irving I, Gutta N, Trotman J, Yeung J, Dunlop L, Hua M, Giri P, Yuen S, Panicker S, Moreton S, Khoo L, Scott A, Kipp D, McQuillan A, McCormack C, Dickinson M, Prince HM. Pralatrexate in relapsed/refractory Tcell lymphoma: a retrospective multicenter study. Leuk Lymphoma. 2021 Feb;62(2):330-6. doi: 10.1080/10428194.2020.1827241.
2. Sharma M, Pro B. Bone Marrow Transplantation for Peripheral T-Cell Non-Hodgkins' Lymphoma in First Remission. Curr Treat Options Oncol. 2015 Jul;16(7):34. doi: 10.1007/s11864-015-0347-3.
3. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, Bartlett NL, Christensen JH, Morschhauser F, Domingo-Domenech E, Rossi G, Kim WS, Feldman T, Lennard A, Belada D, Illés Á, Tobinai K, Tsukasaki K, Yeh SP, Shustov A, Hüttmann A, Savage KJ, Yuen S, Iyer S, Zinzani PL, Hua Z, Little M, Rao S, Woolery J, Manley T, Trümper L; ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019 Jan 19;393(10168):229-40. doi: 10.1016/S0140-6736(18)32984-2.
4. Hong JY, Yoon DH, Yoon SE, Kim SJ, Lee HS, Eom HS, Lee HW, Shin DY, Koh Y, Yoon SS, Jo JC, Kim JS, Kim SJ, Cho SH, Lee WS, Won JH, Kim WS, Suh C. Pralatrexate in patients with recurrent or refractory peripheral T-cell lymphomas: a multicenter retrospective analysis. Sci Rep. 2019 Dec 30;9(1):20302. doi: 10.1038/s41598-019-56891-0.
5. O'Connor OA, Horwitz S, Hamlin P, Portlock C, Moskowitz CH, Sarasohn D, Neylon E, Mastrella J, Hamelers R, Macgregor-Cortelli B, Patterson M, Seshan VE, Sirotnak F, Fleisher M, Mould DR, Saunders M, Zelenetz AD. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol. 2009 Sep 10;27(26):4357-64. doi: 10.1200/JCO.2008.20.8470.
6. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, Lechowicz MJ, Savage KJ, Shustov AR, Gisselbrecht C, Jacobsen E, Zinzani PL, Furman R, Goy A, Haioun C, Crump M, Zain JM, Hsi E, Boyd A, Horwitz S. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011 Mar 20;29(9):1182-9. doi: 10.1200/JCO.2010.29.9024.
7. Advani RH, Ansell SM, Lechowicz MJ, Beaven AW, Loberiza F, Carson KR, Evens AM, Foss F, Horwitz S, Pro B, Pinter-Brown LC, Smith SM, Shustov AR, Savage KJ, Vose JM. A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial. Br J Haematol. 2016 Feb;172(4):535-44. doi: 10.1111/bjh.13855.
8. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, Villa D, Gascoyne RD, Connors JM, Savage KJ. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013 Jun 1;31(16):1970-6. doi: 10.1200/JCO.2012.44.7524.
9. Biasoli I, Cesaretti M, Bellei M, Maiorana A, Bonacorsi G, Quaresima M, Salati M, Federico M, Luminari S. Dismal outcome of T-cell lymphoma patients failing first-line treatment: results of a population-based study from the Modena Cancer Registry. Hematol Oncol. 2015 Sep;33(3):147-51. doi: 10.1002/hon.2144.
10. Hong X, Song Y, Huang H, Bai B, Zhang H, Ke X, Shi Y, Zhu J, Lu G, Liebscher S, Cai C. Pralatrexate in Chinese Patients with Relapsed or Refractory Peripheral T-cell Lymphoma: A Single-arm, Multicenter Study. Target Oncol. 2019 Apr;14(2):149-58. doi: 10.1007/s11523-019-00630-y.
11. Maruyama D, Nagai H, Maeda Y, Nakane T, Shimoyama T, Nakazato T, Sakai R, Ishikawa T, Izutsu K, Ueda R, Tobinai K. Phase I/II study of pralatrexate in Japanese patients with relapsed or refractory peripheral T-cell lymphoma. Cancer Sci. 2017 Oct;108(10):2061-8. doi: 10.1111/cas.13340.
12. Amengual JE, Lichtenstein R, Lue J, Sawas A, Deng C, Lichtenstein E, Khan K, Atkins L, Rada A, Kim HA, Chiuzan C, Kalac M, Marchi E, Falchi L, Francescone MA, Schwartz L, Cremers S, O'Connor OA. A phase 1 study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. Blood. 2018 Jan 25;131(4):397-407. doi: 10.1182/blood-2017-09-806737.
13. Lee SS, Jung SH, Ahn JS, Kim YK, Cho MS, Jung SY, Lee JJ, Kim HJ, Yang DH. Pralatrexate in Combination with Bortezomib for Relapsed or Refractory Peripheral T Cell Lymphoma in 5 Elderly Patients. J Korean Med Sci. 2016 Jul;31(7):1160-3. doi: 10.3346/jkms.2016.31.7.1160.
14. Toner LE, Vrhovac R, Smith EA, Gardner J, Heaney M, Gonen M, Teruya-Feldstein J, Sirotnak F, O'Connor OA. The schedule-dependent effects of the novel antifolate pralatrexate and gemcitabine are superior to methotrexate and cytarabine in models of human nonHodgkin's lymphoma. Clin Cancer Res. 2006 Feb 1;12(3 Pt 1):924-32. doi: 10.1158/1078- 0432.CCR-05-0331.
15. Zhu J, Yeoh EM, Maeda Y, Tobinai K. Efficacy and safety of single-agent pralatrexate for treatment of angioimmunoblastic T-cell lymphoma after failure of first line therapy: a pooled analysis. Leuk Lymphoma.2020 Sep;61(9):2145-52. doi: 10.1080/10428194.2020.1765232.
16. Hong JY, Yoon DH, Yoon SE, Kim SJ, Lee HS, Eom HS, Lee HW, Shin DY, Koh Y, Yoon SS, Jo JC, Kim JS, Kim SJ, Cho SH, Lee WS, Won JH, Kim WS, Suh C. Pralatrexate in patients with recurrent or refractory peripheral T-cell lymphomas: a multicenter retrospective analysis. Sci Rep. 2019 Dec 30;9(1):20302. doi: 10.1038/s41598-019-56891-0.