JBUON 2021; 26(4): 1536-1539
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Pralatrexate experience in peripheral T-cell lymphoma: A multicenter retrospective study from Turkey

Mehmet Sinan Dal[1], Alparslan Merdin[1], Mehmet Ali Erkurt[2], Ömer Ekinci[3], Murat Albayrak[4], Sibel Kabukcu Hacıoglu[5], Ayse Kaya[6], Mehmet Hilmi Dogu[7], Fehmi Hindilerden[8], Ahmet Sarici[2], Mustafa Merter[3], Merih Reis Aras[4], Gulsum Akgun Caglıyan[5], Merih Kizil Cakar[1], Ismet Aydogdu[6], Irfan Kuku[2], Serdal Korkmaz[9], Turgay Ulas[10], Bulent Eser[11], Fevzi Altuntas[1,12]

[1]University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Hematology Clinic and Bone Marrow Transplantation Unit, Ankara, Turkey. [2]Inonu University, Department of Hematology, Malatya, Turkey. [3]Firat University, Department of Hematology, Elazig, Turkey. [4]University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Hematology, Ankara, Turkey. [5]Pamukkale University, Department of Hematology, Denizli, Turkey. [6]Celal Bayar University, Department of Hematology, Manisa, Turkey. [7]Istinye University, Liv Hospital Ulus, Department of Hematology, Istanbul, Turkey. [8]University of Health Sciences, Bakirkoy Dr. SadiKonuk Training and Research Hospital, Department of Hematology, Istanbul, Turkey. [9]University of Health Sciences, Kayseri City Training and Research Hospital, Department of Hematology & Apheresis Unit, Kayseri, Turkey. [10]Near East University, School of Medicine, Department of Internal Medicine, Division of Hematology, Nicosia, Cyprus. [11]Medical Park Antalya Hospital, Department of Hematology, Antalya, Turkey. [12]Ankara Yildirim Beyazit University, School of Medicine, Department of Internal Medicine, Division of Hematology, Ankara, Turkey.

Summary

Purpose: *Pralatrexate is a new generation antifolate treatment agent used for the treatment of relapsed or refractory peripheral T-cell lymphomas. This study aims to determine the general characteristics of the patients receiving pralatrexate therapy in Turkey, contributing to the literature on the effectiveness of pralatrexate therapy in peripheral T-cell lymphomas by determining the response levels of such patients to the therapy. The study also attempts to clinically examine the major side effects observed in patients during treatment with pralatrexate.*

Methods: *The study included patients with peripheral T-cell lymphoma followed up in the hematology units of several hospitals in Turkey. Overall, 20 patients aged 18 and over were included in the study.*

Results: *The median age at the time of diagnosis was 58.5 years. PTCL-NOS (Peripheral T-cell lymphoma, not otherwise specified) subtype was in 40% of patients, making the PTCL-NOS the most common subtype in the study. In general, most patients were diagnosed with disease at an advanced stage. Pralatrexate therapy was given to the patients at a median treatment line of 3.5. Pralatrexate dose reduction was required in only 3 patients (15%). Response to pralatrexate therapy with partial remission (PR) and above was observed in 11 (55%) of the patients.*

Conclusion: *Pralatrexate seemed to be a promising novel treatment in relapsed refractory PTCL patients. However, patients receiving pralatrexate should be followed up carefully for skin reactions, mucosal side effects, thrombocytopenia and neutropenia.*

Key words: *pralatrexate, peripheral T-cell lymphoma, multicenter*

Introduction

Antifolate agents have been used in cancer treatment for many years and methotrexate is the best known antifolate anticancer agent. Antifolate therapies disrupt folate-mediated single carbon metabolism and inhibit the enzyme dihydrofolate reductase (DHFR), preventing the conversion of dihy-

Corresponding author: Mehmet Sinan Dal , MD. University of Health Sciences Ankara Oncology Training and Research Hospital, Department of Hematology & Apheresis Unit, Mehmet Akif Ersoy Mahallesi, 13. Cadde, No: 56, Yenimahalle, Ankara, Turkey. Tel: +90 312-3360909-7216, Email: dr.sinandal@gmail.com
Received: 27/12/2020; Accepted: 30/01/2021

drofolate to tetrahydrofolate. Tetrahydrofolates play a role in the synthesis of the amino acids serine, glycine and methionine, as well as in the synthesis of nucleic acid materials like purine and pyrimidine inside the cell. Besides, they are instrumental in DNA and protein methylation. Antifolate therapies, by inhibiting these steps, cause the death of cancer cells and prevent their proliferation. Peripheral T-cell lymphomas (PTCL) are known to have a poor prognosis. Mak et al reported that the median time from diagnosis to relapse or progression after the first treatment was 6.7 months [1]. Therefore, considering that PTCLs have a much worse prognosis than many other types of cancer, novel therapies are urgently needed for their treatment.

Pralatrexate is a new generation dihydrofolate reductase inhibitor used for the treatment of relapsed or refractory PTCLs. In the PROPEL study, the response rate to pralatrexate therapy was reported as 29% (11% complete response/CR and 18% partial response/PR) [2]. This study aimed to determine the general characteristics of the patients receiving pralatrexate therapy in Turkey, contributing to the literature on the effectiveness of pralatrexate therapy in PTCLs by determining the response levels of such patients to therapy. In their comprehensive review of PubMed literature on pralatrexate usage in R/R peripheral T-cell lymphoma, the expert opinion reported by Jennifer CZ et al was that mucositis was the main observed adverse event [3]. This study also attempted to clinically examine the major side effects observed in patients during treatment with pralatrexate.

Methods

The study sample included PTCL patients with available data in their records stored at the Hematology Outpatient Unit of the University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital. The study also included other patients with PTCL followed up in the Hematology Units of some other hospitals in Turkey. The study was multicenter retrospective. Written approval for the study was obtained from the Ethics Committee of the Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (Ethics Committee File Number: 2019-10/417).

Overall, 20 patients aged 18 and over were included in the study. Patients who received no pralatrexate therapy before and those who did not have PTCL were excluded. One of the patients with PTCL-NOS included in the current study had also been reported in a case report published in 2019, as he entered remission after receiving a prolonged pralatrexate therapy [4]. The same patient was also included in the current analyses, since he continued to be followed up as a patient responding to pralatrexate therapy after publication.

The data of the patients were retrospectively analyzed. Patient demographic characteristics such as age and gender were evaluated. The variables including the disease stage at the time of diagnosis, histological disease types, type of chemotherapy received, number of cycles received, at what cycle patients received pralatrexate therapy, and their response to each cycle of chemotherapy were separately analyzed and evaluated. The therapies that patients received before pralatrexate were also evaluated.

Statistics

SPSS 24.00 software package (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for statistical analyses. Categorical descriptive data were presented as frequency distribution and in percentages, while data involving measurements were presented as mean values ±SD and median (largest, smallest values).

Results

The median age at the time of diagnosis was 58.5 years, while 7 (35%) of the patients included in the study were female and 13 (65%) male. It was observed that the disease subtype was PTCL-NOS in 40% of the patients, making PTCL-NOS the most common subtype in the study (Table 1). The cancer at the time of diagnosis was at Stage 3 in 10 (50%) of the patients, Stage 4 in 5 (25%) of the patients, and Stage 2 in 3 (15%) of the patients. Stage 1 disease was detected in only 2 patients (10%). In general, most patients were diagnosed with advanced disease stage.

Thirteen (65%) patients had a history of autologous stem cell transplantation (ASCT), whereas the rest (35%) received no ASCT. None of the patients received allogeneic stem cell transplantation.

Pralatrexate dose reduction was required in only 3 patients (15%). Response to pralatrexate therapy with PR and above was observed in 11 (55%) of the patients (Table 2).

Table 1. Distribution by disease subtypes

Disease subtype	*n*	*%*
Cutaneous T-cell	1	5.0
PTCL-NOS	8	40.0
Cytotoxic type	1	5.0
Sezary	1	5.0
Mycosis fungoides	4	20.0
Anaplastic T-cell	1	5.0
Hepatosplenic gamma delta	1	5.0
Angioimmunoblastic	1	5.0
Other	2	10.0
Total	20	100

Table 2. Response rates to pralatrexate therapy

	n	%
CR	1	5.0
PR	10	50.0
SD	1	5.0
PD	8	40.0
Total	20	100

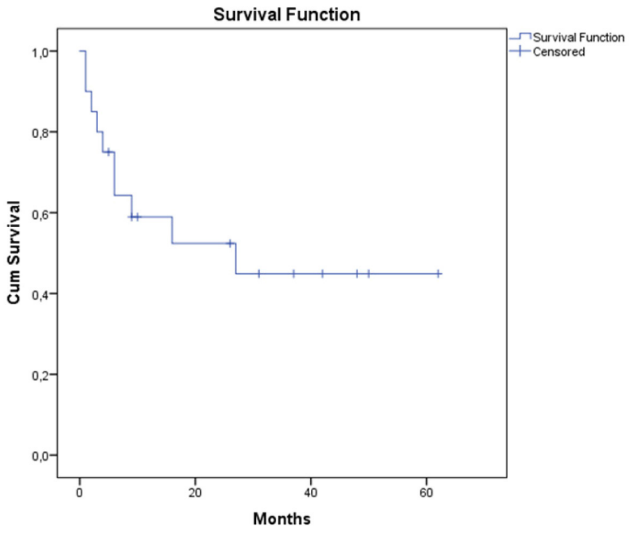

Figure 1. Kaplan-Meier survival analysis in patients who had received pralatrexate.

Stomatitis was observed in 4 patients and thrombocytopenia associated with pralatrexate occurred in 7 patients. Severe rash was observed in 1 patient, nausea in 5 patients, while 15 patients did not report nausea. Diarrhea was observed in 1 patient (5%), constipation in 1 patient (5%), and neutropenia in 8 patients (40%).

Pralatrexate therapy was given to the patients at a median treatment line of 3.5. Autologous stem cell transplantation (ASCT), was also counted as a line of therapy. Median overall survival from the treatment line pralatrexate was found 27 months (Figure 1).

Discussion

CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) has been known as the initial treatment of PTCL for a long time. New agents have been evolving in the treatment of this clinical entity, especially for the relapsed/refractory cases. HDT/ASCT (High-dose therapy/Autologous stem cell transplantation) has also been a major clinical approach for patients who had at least partial response to the induction chemotherapy and were fit for transplantation. In the Nordic Lymphoma Group (NLG) -T-01 study of the NLG, d'Amore et al reported that 44% of treatment-naive PTCL patients were found to have long term progression-free survive (PFS) with dose-dense induction followed by HDT/ASCT treatment [5].

Novel agents have been involved in the treatment of T cell lymphomas. On behalf of (ECHELON-2) Trial, Horwitz et al reported that front-line treatment with A+CHP (Brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone) was superior to CHOP for patients with CD30-positive peripheral T-cell lymphomas [6]. Coiffier et al reported that the objective response rate (ORR) to romidepsin was 25% in relapsed/refractory PTCL patients [7]. On the other hand, Amengual et al showed that the overall response rate to pralatrexate plus romidepsin treatment was 71% (10/14) in PTCL patients [8]. Besides, 60% of our patients had response or stable disease under pralatrexate treatment and this seems to be a promising novel treatment in relapsed refractory PTCL patients. However, our study was a right-censored retrospective study with the analyzed data found in the patient files. Prospective trials stratifying homogeneous patient groups will add more accurate data to the literature.

In conclusion, pralatrexate might be a promising option in relapsed/refractory PTCL patients. Patients receiving pralatrexate should be followed up carefully for skin reactions, mucosal side effects, thrombocytopenia and neutropenia.

Acknowledgements

All authors included in the study approved that they obtained permission from their centers for using data belonging to hospitals where they work. Each author got permission from his/her center individually. The study was approved by the local ethics committee of the Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (Ethics Committee File Number: 2019-10/417). The current working address of the author Alparslan Merdin is ''Hematology Clinic, University of Health Sciences Gülhane Training and Research Hospital, Ankara, Turkey''.

Author contributions

M.S.D. and A.M. designed the study. T.U. and S.K. made the statistical analyses. All authors were data collectors.

Conflict of interests

The authors declare no conflict of interests.

References

1. Mak V, Hamm J, Chhanabhai M et al. 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;31:1970-6.
2. 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.
3. Jennifer CZ, Sara Mohamed J, Salma A, Francine F. Pralatrexate injection for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. Expert Rev Hematol. 2020 Jun;13(6):577-583. doi: 10.1080/17474086.2020.1756257. Epub 2020 Apr 26. PMID: 32293930.
4. Merdin A, İskender D, Ulu B U et al. Pralatrexate induced durable response in a relapsed/refractory peripheral T-cell lymphoma patient with a history of autologous stem cell transplantation: Case report of a patient followed-up over 3 years under pralatrexate treatment. Medicine (Baltimore). 2019;98:e16482. doi:10.1097/MD.0000000000016482
5. d'Amore F, Relander T, Lauritzsen GF et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 2012;30:3093-9. doi:10.1200/JCO.2011.40.2719
6. Horwitz S, O'Connor O A, 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;393:229-40. DOI:https://doi.org/10.1016/S0140-6736(18)32984-2
7. Coiffier B, Pro B, Prince H M et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol 2014;7:11. doi:10.1186/1756-8722-7-11
8. Amengual J E, Lichtenstein R, Lue J et al. A phase 1 study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. Blood 2018;131:397-407. doi:10.1182/blood-2017-09-806737