

# 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

Alparslan Merdin, MD<sup>a,\*</sup>, Dicle İskender, MD<sup>a</sup>, Bahar Uncu Ulu, MD<sup>a</sup>, Mehmet Doğan, MD<sup>b</sup>, Merih Kızıl Çakar, MD<sup>a</sup>, Mehmet Sinan Dal, MD<sup>a</sup>, Fevzi Altuntaş, MD<sup>a</sup>

### Abstract

**Rationale:** Relapsed or refractory peripheral T-cell lymphomas are aggressive diseases. Pralatrexate is an antimetabolite. Hereby, we are reporting a pralatrexate induced durable response in a relapsed/refractory peripheral T-Cell lymphoma patient with a history of autologous stem cell transplantation.

**Patient concerns:** A male patient born in February 1947 was diagnosed with lymphoma based on his cervical lymph node excisional biopsy.

**Diagnoses:** He was diagnosed with PTCL-NOS on February 19, 2013.

**Interventions:** The patient received 6 cycles of CHOP (Cyclophosphamide, doxorubicine, vincristine, methylprednisolone) chemotherapy, which achieved a complete remission. The patient underwent autologous stem cell transplantation in December 2013. After relapse was detected in the third month of the transplantation, the patient was treated with 2 cycles of ViGePP (vinorelbine, gemcitabine, procarbazine, prednisone/ methylprednisolone) chemotherapy. The patient was considered refractory to treatment after the ViGePP chemotherapy, and he was given brentuximab vedotin. Once a full response to treatment was achieved after 2 cycles, the patient received 6 cycles of brentuximab vedotin treatment. After 6 cycles, a skin biopsy was performed and the patient was diagnosed with relapsed/refractory PTCL-NOS. Pralatrexate therapy was then started on February 1, 2016 at a dose of 30 mg/m<sup>2</sup> once weekly for 6 weeks in 7-week cycles.

**Outcomes:** The patient responded to pralatrexate treatment. And he has been under pralatrexate treatment over 3 years.

**Lessons:** Pralatrexate should also be kept in mind as a treatment alternative in relapsed or refractory peripheral T-cell lymphoma patients.

**Abbreviations:** ALCL = anaplastic large cell lymphoma, ASCT = autologous stem cell transplantation, DS = Deauville Score, DSHNHL = German High-Grade Non-Hodgkin Lymphoma Study Group, FDG = fluorodeoxyglucose, LAP = lymphadenopathy, MRI = magnetic resonance imaging, NKTCL = natural killer/T-cell lymphoma, PET/CT = positron emission tomography/computed tomography, PROPEL = pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma, PTCL = peripheral T-cell lymphoma, PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified, SUVmax = maximum standardized uptake value.

**Keywords:** peripheral T-cell lymphoma, pralatrexate, PTCL-NOS, response

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Patient has provided informed consent for publication of the case. And official permission from the hospital was also taken. Alparslan Merdin is the main author of this case report.

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<sup>a</sup> Hematology Clinic and Bone Marrow Transplantation Unit, University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Education and Research Hospital, Ankara, Turkey, <sup>b</sup> Department of Pathology, University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Education and Research Hospital, Ankara, Turkey.

\* Correspondence: Alparslan Merdin, Ankara Dr. Abdurrahman Yurtaslan Onkoloji Eğitim ve Araştırma Hastanesi Hematoloji Polikliniği, Urankent Ek Binası, Yenimahalle, Ankara, Turkey (e-mail: Alparslanmerdin@yahoo.com).

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## 1. Introduction

Pralatrexate is a novel anti-folate drug. It inhibits the enzyme dihydrofolate reductase. Pralatrexate is an antimetabolite. Antimetabolites impair cell division by interfering with genetic material and they are cell cycle phase specific cancer drugs. Antimetabolites can mimic normal substances within the cell. Folic acid antagonists, pyrimidine antagonists, purine antagonists, and adenosine deaminase inhibitors are subgroups of antimetabolite class drugs. Methotrexate is a well known antifolate agent. 5-Fluorouracil, cytarabine, capecitabine, and gemcitabine are pyrimidine antagonists. 6-Mercaptopurine, 6-thioguanine, nelarabine, cladribine, and fludarabine are purine antagonists. Pentostatin is an adenosine deaminase inhibitor. Rüdiger et al reported that 5-year overall survival in PTCL patients (excluding anaplastic large cell lymphoma (ALCL) patients) treated with doxorubicin (Adriamycin)-containing regimens was 26%.<sup>[1]</sup>

In their analysis of 51 relapsed or refractory PTCL-NOS (Peripheral T-cell lymphoma, not otherwise specified) patients who received another systemic chemotherapy after initial systemic therapy without hematopoietic stem-cell transplantation, Mak et al showed that median overall survival of patients with PTCL-NOS after relapse or progression were 6.5 months.<sup>[2]</sup> On the other hand, O'Connor et al reported the response rate to pralatrexate as 29% (12% CR and 18% PR) in 109 evaluable patients who were enrolled in PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) study.<sup>[3]</sup> Hereby, we are reporting a pralatrexate induced durable response in a relapsed/refractory peripheral T-Cell lymphoma patient with a history of autologous stem cell transplantation. Our patient has been followed up over 3 years under pralatrexate treatment.

## 2. Case report

A male patient born in February 1947 was diagnosed with PTCL-NOS based on his cervical lymph node excisional biopsy. He was diagnosed with PTCL-NOS on February 19, 2013. At the time of diagnosis, no bone marrow infiltration was reported in the bone marrow biopsy. The patient received 6 cycles of CHOP chemotherapy, which achieved a complete remission. The patient underwent autologous stem cell transplantation (ASCT) with BEAM (Carmustine, etoposide, cytarabine, melphalan) regimen in December 2013. After relapse was detected in the third month of the transplantation, the patient was treated with 2 cycles of ViGePP chemotherapy. The patient was considered refractory to treatment after the ViGePP chemotherapy, and he was given brentuximab vedotin (ADCETRIS). Once a full response to treatment was achieved after 2 cycles, the patient received 6 cycles of brentuximab vedotin treatment. After 6 cycles, a skin biopsy was performed and the patient was diagnosed with relapsed/refractory PTCL-NOS. Pralatrexate (Folotylin) therapy was then started on February 1, 2016 at a dose of 30 mg/m<sup>2</sup> once weekly for 6 weeks in 7-week cycles.

In March 2016, the patient's weekly dose was deferred due to the lesions on the penis tip and inside the mouth that were thought to be allergic and then methylprednisolone treatment was applied. On August 22, 2016, the patient received the sixth week dose of the 4th cycle of pralatrexate, and a CT scan of the

abdomen / pelvis / neck / thorax was performed on August 26, 2016. In the CT imaging, the spleen was normal with no pathological LAP (lymphadenopathy). The patient was considered responsive to treatment, so the treatment with pralatrexate was continued. Erythematous lesion was found on the soft palate of the patient in February and in March 2017. In March 2017, a 2 × 1 cm ulcerated lesion was detected on the left foot, and biopsies for the lesion and soft palate were performed, which showed no disease involvement. In May 2017, the patient developed a 2 × 2 cm bullous lesion in the lateral condyle of the left foot, which was thought to be a side effect of pralatrexate chemotherapy. The patient's pralatrexate dose was reduced to a dose of 20 mg/m<sup>2</sup>/week from the first week dose of the 9th cycle. Skin side effects were not seen again once the dose was reduced. The patient received the first week dose of the 9th cycle at the dose of 20 mg/m<sup>2</sup> on May 23, 2017, and first week dose of the 10th cycle at the dose of 20 mg/m<sup>2</sup> on July 18, 2017. After the 6th week dose of 13th cycle of pralatrexate, the patient was admitted to the infectious diseases ward due to pneumonia, so the treatment was interrupted for a short period. In the PET/CT (Positron emission tomography/Computed tomography) taken in March 2018, an area with increased FDG (fluorodeoxyglucose) uptake was observed in the posterior area of the right parotid gland with a Deauville Score (DS) of 2, which could not be distinguished from parotid gland. The same PET/CT scan in March 2018 also showed increased FDG uptake in the right paratracheal millimetric lymph node in mediastinum (SUVmax (maximum standardized uptake value): 2.90, DS: 2). The PET/CT scan also showed increased FDG uptake in the lymph node observed in the paraesophageal area in mediastinum (SUV max: 4.19, DS: 3). Increased FDG uptake was also observed in the lymph node measuring 1.2 × 0.7 cm in the right inguinal region (SUVmax: 2.92, DS: 5?, X?).

The patient received the 6th week pralatrexate dose of 18th cycle on November 12, 2018. The PET/CT taken after the 6th week dose of the 18th cycle showed increased FDG uptake (Deauville score of 3) in the 1 cm (approximately) nodular soft tissue structure area of the right parotis lodge that might be consistent with lymph node. But no other lymph nodes with a Deauville Score of 2 or above were observed in other regions of the body. The patient received the first week dose of pralatrexate of the 19th cycle on December 3, 2018. The cervical MRI (Magnetic resonance imaging) taken after that revealed millimetric non-enhancing lesions, as well as a slight increase in size in the right parotid gland compared to the left parotid gland. Based on the PET/CT scan and MRI results, the patient was accepted as complete remission and the monitoring was continued. The patient received the 6th week dose of pralatrexate of 19th cycle on January 7, 2019.

He is receiving folic acid (Folbiol) 5 mg/day 1 × 1, cyanocobalamin (Dodex) 1000 mcg intramuscular, diltiazem hydrochloride 90 mg at the dose of 1 × 1/day (for approximately 1 year), metformin hydrochloride 1000 mg 2 × 1, and sulfamethoxazole/trimethoprim 800/160 mg 1 × 1 (receiving sulfamethoxazole/trimethoprim only on Monday, Wednesday, and Friday). The patient had also used calcium folinate (Folca) and acetylsalicylic acid previously, but he discontinued these drugs.

Lastly, pralatrexate therapy was sometimes temporarily deferred during the course of treatment due to infections,

response assessment, and some other reasons, but once the condition causing the temporary discontinuation had improved, pralatrexate therapy was resumed. The patient's pralatrexate treatment is still ongoing in February 2019. Thrombocytopenia, neutropenia and/or anemia were also seen in some weeks under paralateraxate treatment.

### 3. Discussion

Peripheral T-cell lymphoma is not an indolent lymphoma. In their study of 1153 cases of PTCL(Peripheral T-cell lymphoma) and NKTCL(Natural killer/T-cell lymphoma), Weisenburger et al reported the 5-year overall survival as 32%.<sup>[4]</sup> Weisenburger et al also found that median age of the 340 patients with PTCL-NOS (PTCL- not otherwise specified) was 60 years old.<sup>[4]</sup> Immediate appropriate treatment should be started after accurate diagnoses of peripheral T cell lymphomas.

Schmitz et al analyzed 70 PTCLU(peripheral T-cell lymphoma, unspecified) patients treated within trials of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) and they found the 3-year overall survival as 53.9%.<sup>[5]</sup> CHOP (Cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone) or CHOEP(Cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone, and etoposide) containing protocols were used in the treatment of those patients.<sup>[5]</sup> In addition, Horwitz et al reported that A+CHP (Brentuximab Vedotin plus cyclophosphamide, doxorubicin, and prednisone) was superior to CHOP for front-line treatment of patients with CD30-positive peripheral T-cell lymphomas.<sup>[6]</sup>

In their intention-to-treat analysis in 252 nodal PTCL and enteropathy-associated T-cell lymphoma patients (excluding anaplastic lymphoma kinase-positive anaplastic large cell lymphoma) from the Swedish Lymphoma Registry, Ellin et al reported that upfront autologous stem cell transplantation was associated with a superior overall survival and progression free survival compared with patients treated without autologous stem cell transplantation.<sup>[7]</sup> Those 252 patients were up to the age of 70 years with history of CHOP or CHOEP treatments.<sup>[7]</sup> Ellin et al also reported the median overall survival after relapse/progression in 211 patients who had partial or complete response to primary treatment as 6 months.<sup>[7]</sup>

In their phase II study of pralatrexate in Japanese patients with relapsed or refractory peripheral T-cell lymphoma, Maruyama et al reported that 9 of 20 evaluable patients (45%) responded to pralatrexate treatment.<sup>[8]</sup> Maruyama et al also found that all of responses to pralatrexate treatment were seen in the first treatment cycle.<sup>[8]</sup> Besides, our relapsed/refractory peripheral T-cell lymphoma patient also responded to pralatrexate treatment. And he has been under pralatrexate treatment over 3 years. In conclusion, pralatrexate should also be kept in mind as a treatment option in relapsed or refractory peripheral T-cell lymphoma patients.

### Author contributions

**Conceptualization:** Alparslan Merdin.

**Data curation:** Alparslan Merdin.

**Formal analysis:** Alparslan Merdin.

**Investigation:** Alparslan Merdin, Mehmet Doğan.

**Methodology:** Alparslan Merdin.

**Project administration:** Alparslan Merdin.

**Software:** Alparslan Merdin.

**Supervision:** Alparslan Merdin, Merih Kızıl Çakar, Fevzi Altuntaş.

**Validation:** Alparslan Merdin, Mehmet Doğan, Merih Kızıl Çakar, Mehmet Sinan Dal, Fevzi Altuntaş.

**Visualization:** Alparslan Merdin, Bahar Uncu Ulu, Merih Kızıl Çakar, Mehmet Sinan Dal, Fevzi Altuntaş.

**Writing – original draft:** Alparslan Merdin, Dicle İskender, Bahar Uncu Ulu, Mehmet Doğan, Merih Kızıl Çakar, Mehmet Sinan Dal, Fevzi Altuntaş.

**Writing – review & editing:** Alparslan Merdin, Dicle İskender, Bahar Uncu Ulu, Mehmet Doğan, Merih Kızıl Çakar, Mehmet Sinan Dal, Fevzi Altuntaş.

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