

Conference Case

Relapsed refractory nodal peripheral T-cell lymphoma with follicular helper T-cell phenotype was initially resistant to pralatrexate and confirmed to be unresponsive to subsequent forodesine, but responded to re-instituted pralatrexate

Keywords: Peripheral T-cell lymphoma (PTCL), Pralatrexate (PDX), Forodesine, Relapse/Refractory, Retreatment

CASE REPORT

The patient was a 79-year-old Japanese female. She developed multiple areas of swelling in the right axilla and bilateral neck lymph nodes (LNs), in addition to loss of appetite and night sweats. She was diagnosed with peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) with Ann Arbor clinical stage of IIIB, International Prognostic Score (IPI) of high intermediate (HI) and prognostic index for PTCL-U (PIT) score of 2. Six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) were administered and complete remission (CR) was confirmed by F18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). After 8 years of remission, she presented with multiple swollen superficial LNs. Left cervical LN biopsy yielded the diagnosis of nodal peripheral T-cell lymphoma with follicular helper T-cell phenotype (nodal PTCL with TFH phenotype) (Figure 1). On immunohistochemistry, the lymphoma cells were positive for CD2, CD3, CD4, CD5, CD7, CD10, PD1 and CCR4, and negative for CD8, CD20 and TIA1. There was no evidence of bone marrow or CNS invasion. She was administered 6 cycles of CVP (cyclophosphamide, vincristine and prednisolone), resulting in CR, but she presented again with multiple superficially swollen LNs 7 months after the first relapse. Lymph node biopsy yielded the diagnosis of relapsed nodal PTCL with TFH phenotype and mogamulizumab (1 mg/kg) was started. The LNs transiently decreased in size but became swollen again just prior to completion of the first cycle. Therefore, she was started on pralatrexate (PDX) at 30 mg/m². As reduction of the swollen LNs was evident during the initial cycle of the new regimen, PDX was continued for a second cycle. However, the LNs started to increase in size again and only a reduction in the size of the swollen axillary LNs was evident. The regimen was switched to forodesine at 600 mg/day, which exacerbated the disease. As the efficacy of PDX was maintained for some lesions (e.g., swollen axillary LNs), forodesine was switched again to PDX at 30 mg/m². The LNs rapidly decreased in size in response to PDX. As she developed severe stomatitis

(grade 4 according to CTCAE version 4.0) after the second dose, PDX was discontinued. She died of concurrent pneumonia 18 months after the first relapse. No swollen LNs were found on postmortem examination; PDX response was rated as CR.

PTCL is an aggressive, heterogeneous disease that includes many subtypes of mature T- and natural killer-cell neoplasms, and accounts for 5-10% of all non-Hodgkin lymphomas in North America and Europe.¹ The disease often accounts for a higher percentage of cases, i.e., approximately 20% in Asia, including Japan.² No standard treatment has been established. CHOP or CHOP-like regimens are often selected for initial treatment.³ The CR rate ranges from 50% to 70%, but relapse is not infrequent and the long-term prognosis is unfavorable.¹ The median survival time after relapse is poor, i.e., only 5.5 to 6 months;⁴ therefore, countermeasures to treat relapse are urgently needed. Chihara and colleagues reported that the long-term prognosis improves after hematopoietic stem cell transplantation (SCT) in post-relapse PTCL.⁵ The 5-year survival rate was 32% in patients with autologous SCT, 52% with allogeneic SCT and 10% without SCT. New drugs have become available in recent years for the treatment of recurrent PTCL. They include pralatrexate,⁶ forodesine,⁷ romidepsin,⁸ mogamulizumab⁹ and brentuximab.¹⁰ Regarding the effects of these drugs, the overall response rate (ORR) of 0 to 54%,⁶⁻¹⁰ median response duration of 3 to 28 months and median survival time of 6 to 14.5 months are unsatisfactory. The only method to obtain a long-term sustained response was considered to be the successive use of these new drugs in clinical practice. However, there is no evidence regarding proper use of these new drug regimens. It also remains unclear how the therapeutic response and pharmacological effects vary with the sequence of use of new drug regimens. In this case, re-instituted PDX was effective, although the underlying reason remains unclear. The possibility that forodesine affected on the pharmacological effects of PDX cannot be excluded because the response to the re-instituted PDX occurred after forodesine. As for adverse events, stomatitis, which did not develop during the initial therapy with PDX, developed in a

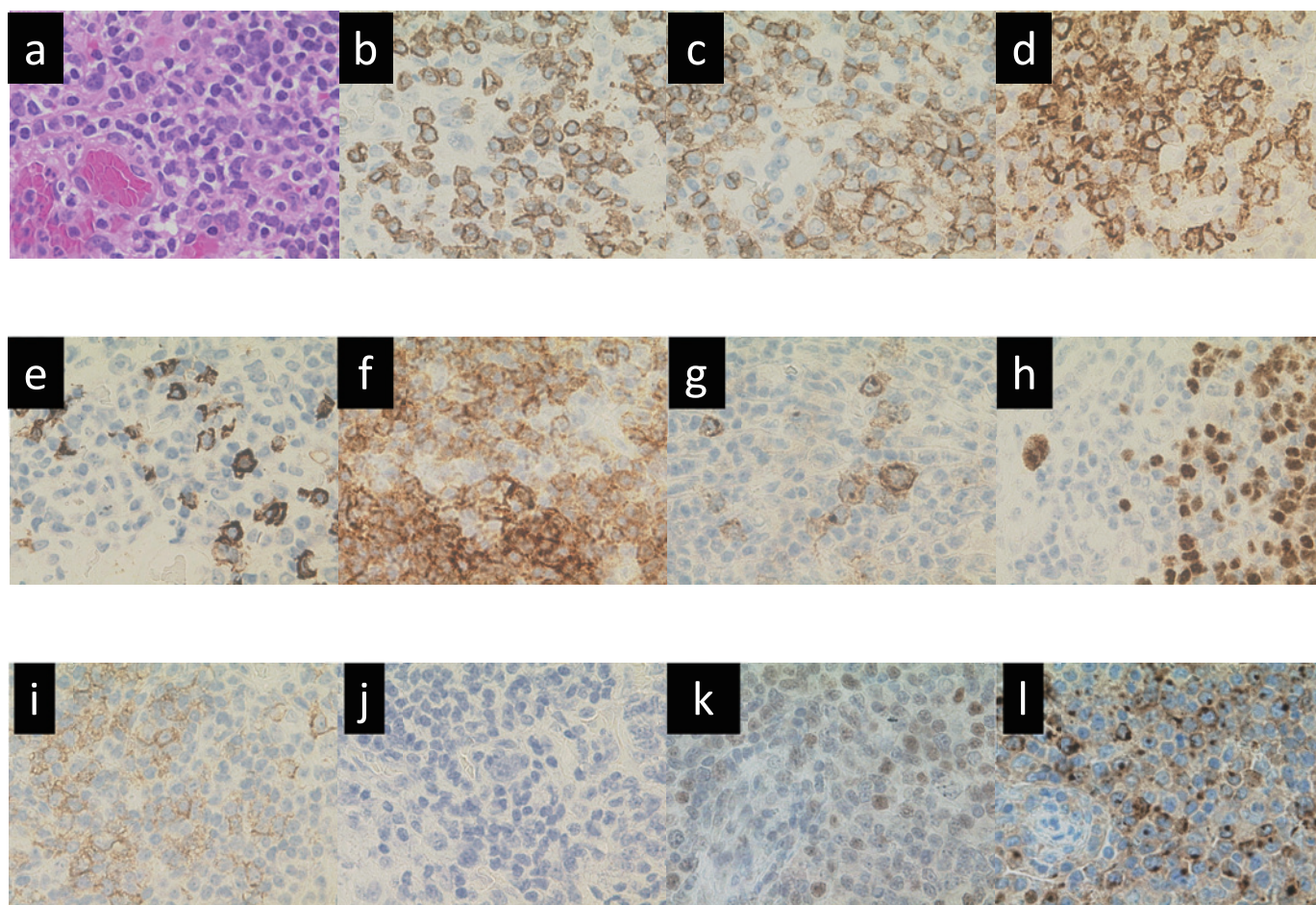


Fig. 1. Lymph node in the first relapse ($\times 400$)

Sheet-like growth of medium-to-large atypical cells with irregular nuclear shapes was observed (**a**, HE). On immunohistochemistry, the lymphoma cells were CD3-positive (**b**), CD4-positive (**c**), CD10-focally positive (**d**), CD20-negative (**e**), PD1-focally positive (**f**), EBER-negative (**g**), BCL6-positive (**k**) and CXCL13-positive (**i**). Proliferation of follicular dendritic cells (FDC) was noted on immunohistochemistry with CD21 (**j**). Hodgkin-Reed Sternberg-like B-cells were positive for CD30 (**g**) and PAX-5 (**h**).

severe form following re-institution of PDX. Furthermore, it was thought to be important to prevent the development of infections due to neutropenia and lymphopenia. In an *in vitro* study reported by Oiwa *et al.*, a PTCL cell line that had become resistant to PDX after exposure to PDX exhibited increased susceptibility to forodesine, although the underlying reason remained unclear.¹¹ However, exposure to the drugs was in the reverse sequence in the present case. Thus, the possibility that PDX and forodesine affect the pharmacological effects of each other cannot be excluded.

CONFLICT OF INTEREST

Disclosure of conflict of interest: None.

REFERENCES

- Vose J, Armitage J, Weisenburger D; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol.* 2008; 26 : 4124-4130.
- Park S, Ko YH. Peripheral T cell lymphoma in Asia. *Int J Hematol.* 2014; 99 : 227-239.
- NCCN Clinical practice guidelines in oncology. T-cell lymphomas Version 3. 2018. <http://WWW.nccn.org>. Accessed 9 August 2018.
- Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood.* 2014; 124 : 1570-1577.
- Chihara D, Fanale MA, Miranda RN, *et al.* The survival outcome of patients with relapsed/refractory peripheral T-cell lymphoma-not otherwise specified and angioimmunoblastic T-cell lymphoma. *Br J Haematol.* 2017; 176 : 750-758.
- 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 : 1182-1189.
- Makita S, Maeshima AM, Maruyama D, Izutsu K, Tobinai K. Forodesine in the treatment of relapsed/refractory peripheral T-cell lymphoma: an evidence-based review. *OncoTargets Ther.* 2018; 11 : 2287-2293.
- Maruyama D, Tobinai K, Ogura M, *et al.* Romidepsin in Japanese patients with relapsed or refractory peripheral T-cell

- lymphoma: a phase I/II and pharmacokinetics study. *Int J Hematol.* 2017; 106 : 655-665.
- 9 Ogura M, Ishida T, Hatake K, *et al.* Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-CC chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *J Clin Oncol.* 2014; 32 : 1157-1163.
 - 10 Pro B, Advani R, Brice P, *et al.* Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. *Blood.* 2017; 130 : 2709-2717.
 - 11 Oiwa K, Hosono N, Nishi R, O'Connor O, Yamauchi T. Generation and Characterization of pralatrexate-resistant cell line. 10th Annual T-cell lymphoma forum.

**Yasunobu Sekiguchi,¹⁾ Mutsumi Wakabayashi,¹⁾
Haruko Takizawa,¹⁾ Hiroko Iizuka,¹⁾
Sakura Sakajiri,¹⁾ Keiji Sugimoto,¹⁾
Tadaaki Inano,²⁾ Yasutaka Fukuda,²⁾
Yasuharu Hamano,²⁾ Shigeki Tomita,³⁾
Hiroshi Izumi,³⁾ Mitsuo Okubo,⁴⁾
Noriko Nakamura,⁵⁾ Tomohiro Sawada,⁵⁾
Norio Komatsu,²⁾ Masaaki Noguchi¹⁾**

¹⁾Department of Hematology, Urayasu-shi, Japan, ³⁾Division of Diagnostic Pathology, Urayasu-shi, Japan, ⁴⁾Laboratory of Blood Transfusion, Urayasu-shi, Japan, ⁵⁾Department of Laboratory Medicine, Juntendo University Urayasu Hospital, Urayasu-shi, Japan, ²⁾Department of Hematology, Juntendo University Hospital Bunkyo-ku, Japan
Corresponding author: Yasunobu Sekiguchi, Department of Hematology, Juntendo University Urayasu Hospital, 1-1, Tomioka 2-chome, Urayasu, Chiba Prefecture.
E-mail: yasu_sek@juntendo-urayasu.jp


Received: August 28, 2018.

Accepted: January 15, 2020.

Online Published: March 28, 2020

DOI:10.3960/jslrt.18031

Copyright © 2020 The Japanese Society for Lymphoreticular Tissue Research

 This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

EXPERT'S COMMENT

Treatment options for peripheral T-cell lymphomas (PTCLs) have increased with the emergence of several new drugs in recent years; however, none have been established as a standard treatment based on randomized clinical trials. In the current case report, re-challenge with pralatrexate (10-propargyl-10-deazaaminopterin; PDX) after forodesine failure induced a response in a patient with relapsed PTCL not otherwise specified. The mechanism of this phenomenon remains unclear; however, I would like to propose a possible mechanism based on: i) the theoretical principles of cancer growth models, ii) the mechanism of action of each drug and iii) the drug concentration in the blood.

Alternating therapy is a reasonable treatment strategy based on the Goldie–Coldman hypothesis.¹ According to this hypothesis, the probability that cancer contains drug-resistant clones depends on the mutation rate and size of the tumor. Combination chemotherapy is the best strategy to overcome resistance, as it enables the administration of many drugs at an early stage. Although combination drug treatments can be intolerable due to toxicity, alternating therapy enables the administration of multiple non-cross-resistant drugs with tolerable toxicity. In this case, a reduction in the tumor was observed after PDX rechallenge following the failure of forodesine treatment. Forodesine may have some effect on PDX-sensitive clones.

PDX is a novel antifolate that was designed specifically to have a high affinity for the reduced folate carrier, which efficiently internalizes natural folates and antifolates, and has been demonstrated to be highly active in T-cell lymphoma.² In contrast, forodesine is a novel purine nucleoside phosphorylase (PNP) inhibitor. Preclinical studies revealed that PNP deficiency increases the dGuo concentrations in plasma and T-cells.³ An increased concentration of dGuo results in the accumulation of deoxyguanosine triphosphate. This in turn causes an imbalance in the deoxynucleotide pool, which reduces ribonucleotide reductase activity, leading to T-cell apoptosis. This imbalance may increase the anti-tumor activity of PDX.

In the current case, rechallenge with PDX induced both a strong adverse event and an anti-tumor response. This suggests that the blood PDX concentration was high, leading to

both desirable and undesirable effects. Although the blood concentration of PTX was not measured, forodesine may have affected its concentration. Dose-adjusted (DA)-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) therapy resulted in relatively higher response and survival rates (response rate, 78%; 2-year progression-free survival rate, 62.5%; and 2-year overall survival rate, 82.4%) in untreated patients with PTCL than a CHOP (cyclophosphamide, prednisone, vincristine and hydroxyl doxorubicin) regimen.⁴ DA-EPOCH has been used in dose-adjustment strategies based on the hematopoietic nadir, where pharmacokinetic analyses of etoposide and doxorubicin revealed significant interpatient variation in steady-state plasma concentrations. This strategy is reasonable when there is a sufficient blood concentration.

It will be necessary to develop a regimen with acceptable toxicity based on simultaneous or sequential use of drugs with different non-cross-resistance or different mechanisms of action to achieve stronger antitumor effects. The results of further clinical trials are keenly awaited.

REFERENCES

- 1 Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep.* 1979; 63 : 1727-1733.
- 2 Maruyama D, Nagai H, Maeda Y, *et al.* Phase I/ II study of pralatrexate in Japanese patients with relapsed or refractory peripheral T-cell lymphoma. *Cancer Sci.* 2017; 108 : 2061-2068.
- 3 Carson DA, Kaye J, Seegmiller JE. Lymphospecific toxicity in adenosine deaminase deficiency and purine nucleoside phosphorylase deficiency: possible role of nucleoside kinase(s). *Proc Natl Acad Sci USA.* 1977; 74 : 5677-5681.
- 4 Maeda Y, Nishimori H, Yoshida I, *et al.* Dose-adjusted EPOCH chemotherapy for untreated peripheral T-cell lymphomas: a multicenter phase II trial of West-JHOG PTCL0707. *Haematologica.* 2017; 102 : 2097-2103.

Hisakazu Nishimori

Department of Hematology and Oncology,
Okayama University Hospital
E-mail: n-mori@md.okayama-u.ac.jp