Case Reports in Oncology

Case Rep Oncol 2019;12:529–536

DOI: 10.1159/000501070
Published online: July 16, 2019

Case Report

Pralatrexate for Prolonged Treatment of Refractory Peripheral T-Cell Lymphoma, Not Otherwise Specified, with Prophylactic Leucovorin

Koichi Kitazume Yuri Akagawa Sachie Wada Takayuki Suzuki Akira Fujita

Department of Hematology, Showa General Hospital, Kodaira-City, Japan

Keywords
Pralatrexate · Refractory PTCL-NOS · Leucovorin

Abstract
Peripheral T-cell lymphomas (PTCLs) are a rare and heterogenous group of hematological malignancies involving T or NK cells. PTCLs are generally associated with an aggressive course and poor prognosis. Pralatrexate (PDX) is the first FDA-approved agent for the treatment of refractory/recurrent PTCL. It has single-agent activity against PTCLs; however, oral mucositis represents dose-limiting toxicity in clinical practice. We report on the case of a patient administered with modified THP-COP therapy (pirarubicin [tetrahydropyranyl adriamycin], cyclophosphamide, and prednisone), who had bone or bone marrow as the primary lesion, which was treated successfully with PDX for an extended period of 1 year, with prophylactic use of leucovorin for oral mucositis. The maintenance dose of PDX was 30 mg/m^2 IV, over 3 consecutive weeks dosing with a 1-week rest period due to bone marrow suppression. The patient also received leucovorin 5 mg PO 3 times daily from days 2 to 6 after each PDX administration. Disease activity was well controlled, stable, and no oral mucositis was observed over the course of treatment.

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Koichi Kitazume
Department of Hematology, Showa General Hospital
8–1-1 Hanakoganei
Kodaira-City, Tokyo 187–8510 (Japan)
E-Mail k3-kitazume@showa-hp.jp

Introduction

Peripheral T-cell lymphoma (PTCL) is a group of diseases where mature T/NK cells become cancerous. PTCL accounts for approximately 10% of all non-Hodgkin lymphomas [1]. In Japan, there are 2,000–3,000 patients with peripheral and cutaneous T-cell lymphomas, with a crude prevalence of 2.0 per 100,000 (except adult T-cell leukemia [ATL], which is peculiar to Japan) [2]. The global incidence is also low. The 2016 WHO classification scheme lists 29 types of the disease, based on their biochemical and genetic features and predominantly involved organs. One of these, PTCL-NOS, is not otherwise classified and is the second most common type in Japan, after ATL [3, 4].

The primary treatment for PTCL is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy and has a response rate of 50–65%. However, patients who are resistant to therapy have an extremely poor prognosis, with a median overall survival of 2.5–5.8 months and a 1-year survival rate of approximately 25% [5–7]. A standard second-line salvage therapy for relapsed or refractory PTCL has not been established; however, combination chemotherapy, pralatrexate (PDX), brentuximab, romidepsin, and others are used [8].

PDX is an antifolate that was approved by the FDA in 2009 for the treatment of relapsed or refractory PTCL, and was launched in Japan in 2017. PDX is administered over weekly IV infusions for 6 weeks, followed by 1-week drug holidays between cycles. Then this cycle is repeated with subsequent dosage changes determined by the patient's condition. Stomatitis is the most common side effect of PDX and its dose-limiting toxicity causes many patients to drop out early in treatment. Other adverse effects include myelosuppression and infection [9, 10]. There are few case reports of PDX due to the small number of patients who receive the drug, and its recent approval.

We describe a patient with PTCL-NOS that was refractory to modified THP-COP therapy comprising pirarubicin (tetrahydropyranyl adriamycin [THP]), cyclophosphamide, and prednisone. The patient achieved remission with PDX monotherapy, a modified regimen of O'Connor et al. [11] and remission was maintained for more than 1 year.

History

A 72-year-old Japanese male was positive for fecal occult blood during a medical examination in April 2017, and was subsequently diagnosed with adenocarcinoma, suspicious for group 4 by biopsy. Whole-body examination consisted of computed tomography and 18F-FDG-PET/CT (PET), and PET revealed slight uptake in the lymph nodes and extensive uptake in the spine (Fig. 1a). However, no other metastatic lesions were found. From these results, we suspected spinal disease, metastasis, malignant lymphoma, and multiple myeloma.

His previous medical history was significant for jejunum rupture (at age 52), postoperative ileus (at 53) and colorectal cancer (at 72 years-old, ESD was performed). His only comorbidity was lumbar herniation beginning at age 60. He had a family history of lung and prostate cancer (father) as well as uterine cancer and cerebral hemorrhage (mother).

Clinical Presentation and Diagnosis

Figure 2 shows the patient's diagnosis and clinical course. His main complaint was backache. On examination, his height was 169.7 cm, weight 67.4 kg, body temperature 36.7°C, blood pressure 134/82 mm Hg, and pulse 71 bpm. No anemia or jaundice was observed in his conjunctiva. No abnormalities were found during full-body examination, including the superficial lymph nodes, with the exception of a 10 cm long abdominal operative scar. His blood tests showed normal ranges of Hb (14 g/dL), red blood cells (462 × 10^4/μL), hematocrit

(42.2%), and platelets (12.5 × 10^4/μL). His white blood cells (WBC) were elevated to 84 × 10^2/μL with increased neutrophils (75.3%). No atypical cells were identified in the blood. Biochemical examination revealed high soluble IL-2R (835 U/mL; reference range 121–613) and normal lactate dehydrogenase (LDH) (202 IU/L; reference range: 106–211). Chest X-ray showed no abnormalities.

He was definitively diagnosed with non-Hodgkin's lymphoma by bone marrow biopsy. Pathological examination of bone marrow aspirate from the left ilium revealed a lesion throughout approximately half of the sample. The lesion was composed of small lymphocytes with irregular-shaped nuclei, histiocytes with large nuclei and eosinophils, and no normal hematopoietic cells. The lymphocytes were immunohistologically positive for CD45. Most of the small cells were CD3+, CD5+ and UCHL+ T cells, and the majority were CD4+. Medium-sized atypical lymphocytes proliferated diffusely and were positive for CD3 and CD4, but negative for CD20, CD30, PAX5 and EBER, suggesting PTCL-NOS as a classification.

Karyotyping revealed a reciprocal translocation t(3;4)(p21;p16) of chromosomes 3 and 4 in one of 20 cells.

Magnetic resonance imaging (MRI) revealed multiple regions (multiple bone infiltrates including vertebrae, sternum, ribs, and bone walls) with high-signal intensities in the cervical to lumbar vertebra and sacrum. The vertebral cortex appeared destroyed at the Th11 level. We suspected infiltration of lymphoma from the bone cortex to the side of the spinal canal at Th12, and slightly, at the bilateral intervertebral foramina of Th12/L1 (Fig. 3a). Based on these results, we diagnosed him with primary PTCL-NOS originating from the bone marrow/bone.

His International Prognostic Index (IPI) score placed him in the high-intermediate risk group (clinical stage 4, age 71 > 60 years, LDH 202 < upper limit of reference range, ECOG performance status [PS] 0, extranodal sites > [1]), and his Prognostic Index for PTCL [PIT] indicated the high-intermediate risk group [group 3] (age 71, LDH 202, PS 0, bone marrow invasion [+]).

Clinical Course

As first-line therapy, we initiated modified THP-COP therapy (cyclophosphamide 1,200 mg [90%], pirarubicin 80 mg [90%], prednisolone 60 mg day 1–5) 2 times, every 4 weeks beginning in August 2017 (Fig. 2). Vincristine was removed from the regimen because the patient had a history of colorectal cancer. In the first follow-up MRI, we noted slightly reduced invasion of the vertebral body, but no apparent change in other sites. Therefore, higher doses of cyclophosphamide 1,300 mg (97%) and pirarubicin 90 mg (101%) and the same dose of prednisolone were administered 4 times (total 6 times). During this therapy, myelosuppression (WBC count 1,300/μL) and nausea occurred and were treated with G-CSF and palonosetron, respectively. His backache improved. The follow-up PET/CT after the fourth cycle showed elimination of lymph node accumulation (Fig. 1b). Although accumulation remained in the skeletal bones, the number of uptake regions and uptake level decreased in comparison with the levels observed at initial diagnosis. On his follow-up MRI after sixth cycle, the signals disappeared within the non-bone regions, and high signals in the vertebral body were reduced slightly. However, signal abnormalities and abnormal enhancements still occurred frequently in thoracolumbar and sacral vertebrae (Fig. 3b). LDH was 213 IU/L and soluble IL-2R 572 U/mL. Zoledronate therapy was initiated to control bone lesion progression.

Because of his inadequate response to the first-line chemotherapy, we changed to PDX alone as second-line therapy in February 2018 (Fig. 2). When administering PDX, we also performed cryotherapy, and administered concomitant oral leucovorin (LV) 5 mg, 3 times daily for 4 days, beginning the next day, and subcutaneous injections of vitamin B12 once every

2–3 months to prevent stomatitis [11]. PDX was administered once weekly. The starting dose was 10 mg/m^2 and escalated each week to 20, then 30 mg/m^2. At the maximum dose of 30 mg/m^2, we prolonged LV administration to 5 days. Four weeks after initiation of PDX therapy, his LDH was unchanged (214 IU/L), but his soluble IL-2R dropped to 237 U/mL, within the reference range. His WBC count recovered slowly (3,100/μL), and his anemia became mild. Thereafter, he continued to receive outpatient treatment with a 3-week administration of PDX at the same dose, followed by a 1-week drug-holiday. Follow-up MRI in June showed reduced infiltrates in the vertebral body of Th11 and 12, and no relapses were observed, even after the 28th administration of PDX in November (Fig. 3c). The most recent LDH and soluble IL-2R levels were 219 IU/L and 265 U/mL, respectively, in February 2019. Currently, the patient remains in good condition and no adverse reactions like stomatitis have been observed.

Discussion/Conclusion

We diagnosed the patient with a bone or bone marrow-originated lymphoma because small lymph node swelling was observed at initial diagnosis. We diagnosed PTCL-NOS by bone marrow pathology, and reciprocal translocations of chromosome 3 and 4 of T lymphocytes t(3;4)(p21;p16) were identified. As this karyotype has never been reported, its detailed carcinogenic mechanisms are unknown. Moreover, there are few reports of malignant lymphoma originating in the bone or bone marrow and therapies to treat such a lymphoma are not established. The patient had a poor prognosis with stage IV, IPI high-intermediate risk and PIT group 3. His nodal tumors disappeared after first-line therapy, with residual high FDG uptake in Th 11 and 12. While his LDH level was slightly over the upper limit of the reference range, his soluble IL-2R level stabilized at a low level within the reference range. He achieved partial remission with PDX monotherapy as salvage treatment and has maintained a stable state for 1 year in ambulatory care settings.

The prognosis of refractory PTCL is extremely poor. PDX was the first FDA-approved drug in the world based on the prospective pivotal trial (PROPEL study) [9] in patients with relapsed or refractory PTCL [12]. A case-matched analysis of the PROPEL trial demonstrated that PDX increased overall survival with a hazard ratio of 0.432 compared with a retrospectively recruited control group receiving second-line chemotherapy other than PDX [13]. Additionally, regardless of the number of prior treatments, the overall response rate and complete remission rates are similarly improved; the smaller the number of prior treatments, the longer the progression-free survival and response duration of response, suggesting that earlier administration of PDX may be beneficial [13]. On the other hand, due the side effects of PDX, only 68% of patients in the PROPEL study maintained cycles of 30 mg/m^2 for 6 weeks, with 1 week off treatment (7 weeks) [9]. The therapeutic effects of PDX were also demonstrated in a Japanese clinical study; however, 88% of cases exhibited dose skipping due to adverse events [10]. Therefore, prevention of side effects and dose adjustment are important for continued administration of PDX. In the present case, our use of a 3-week on/1-week off treatment prevented hematotoxicity over a 1 year course of administration.

Regular administration of vitamin B12 and folic acid before and after PDX is recommended to prevent side effects [12]. In a Japanese Phase I/II study, stomatitis was the most common side effect of PDX, with an incidence as high as 88%, despite the use of vitamin B12 and folic acid (1 mg, PO) [10]. Stomatitis developed due to a deficiency in the active form of folic acid (tetrahydrofolate, THF) through inhibition of the folate-metabolizing enzyme dihydrofolate reductase by PDX. In contrast, metabolism of leucovorin (i.e., 5-formyl-THF) was not

affected by PDX, because it is incorporated into the cellular folate pool and is non-enzymatically converted into active THF. Therefore, we used LV, available in Japan as a medicine for prevention and treatment of antifolate-related toxicities. However, since an overdose of leucovorin may attenuate the effects of PDX dosage is important. Koch et al. reported that leucovorin prevented stomatitis without compromising the efficacy of PDX in patients with transformed Mycosis Fungoides [14, 15], as did Foss et al. for patients with cutaneous T-cell lymphoma [14, 15]. They prescribed leucovorin 15 mg or 50 mg every 6 h for 2–6 doses starting 24 h after PDX 30 mg/m^2 administration. We determined LV dosage considering patients' convenience and its minimal influence on the antitumor efficacy of PDX. LV was started at 5 mg 3 times daily for 4 days with doses of 10 and 20 mg/m^2 of PDX. PDX treatment duration was then increased to 5 days at a dose of 30 mg/m^2. This dosage regimen of LV prevented stomatitis completely. Although LV appears effective, its efficacy within the context of PDX therapy requires confirmation to optimize dosage.

We experienced a case of long-term disease control with PDX monotherapy as a second-line therapy in a patient with refractory PTCL-NOS and a poor prognosis. To continue PDX monotherapy over time, the administration period of LV should be adjusted to reduce PDX-related adverse events, including stomatitis and hematotoxicity.

Acknowledgements

We would like to thank Dr. Hiroyuki Miyoshi and Dr. Koichi Ohshima of the Department of Pathology, Kurume University School of Medicine for conducting pathological diagnosis of bone marrow specimens in this study. We also thank the Wysiwig Co., Ltd. for editing assistance.

Statement of Ethics

The patient included in this study has provided written informed consent to publish the images, and the authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

Financial support for medical translation and writing was provided by Mundipharma K.K.

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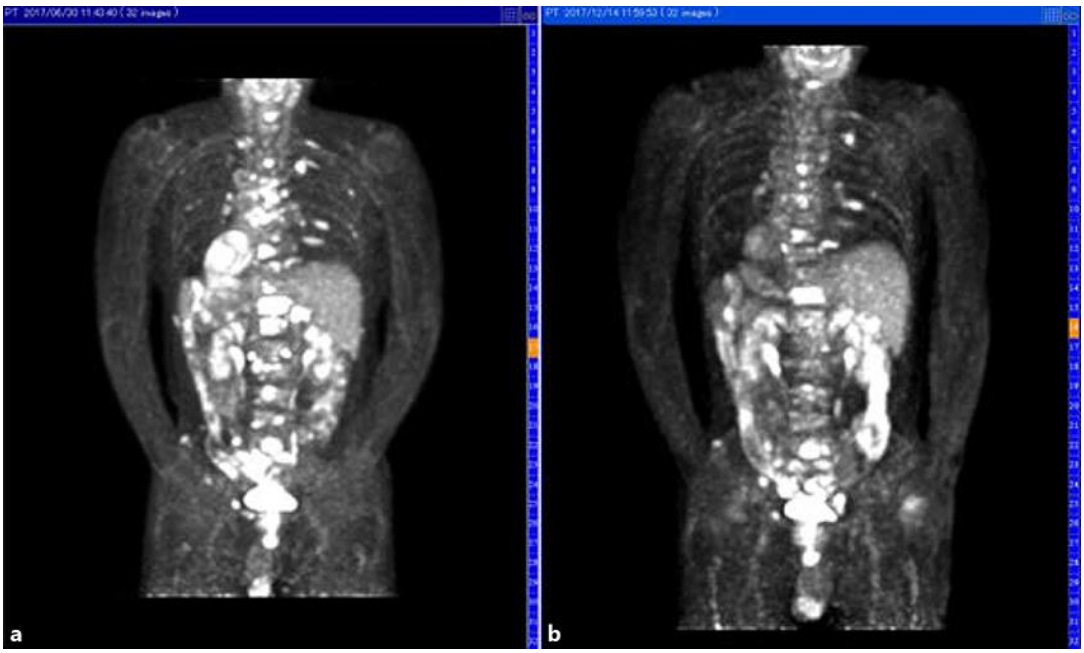

Fig. 1. 18F-FDG-PET. Initial diagnosis (**a**). After 4 cycles of modified THP-COP treatment (**b**), accumulation in the lymph node disappeared and standardized uptake value max in Th 12 decreased from 7.2 to 5.4.

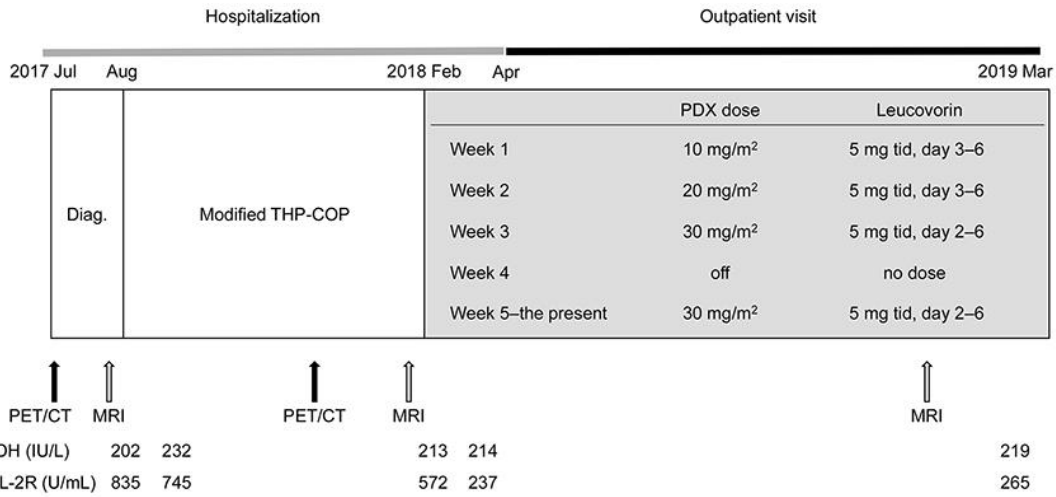

Fig. 2. Treatment schedule for PTCL. Modified THP-COP (cyclophosphamide 1,200 mg [90%], pirarubicin 80 mg [90%], prednisolone 60 mg day 1–5). LDH, lactate dehydrogenase; PDX, pralatrexate; sIL-2R, soluble interleukin-2 receptor.

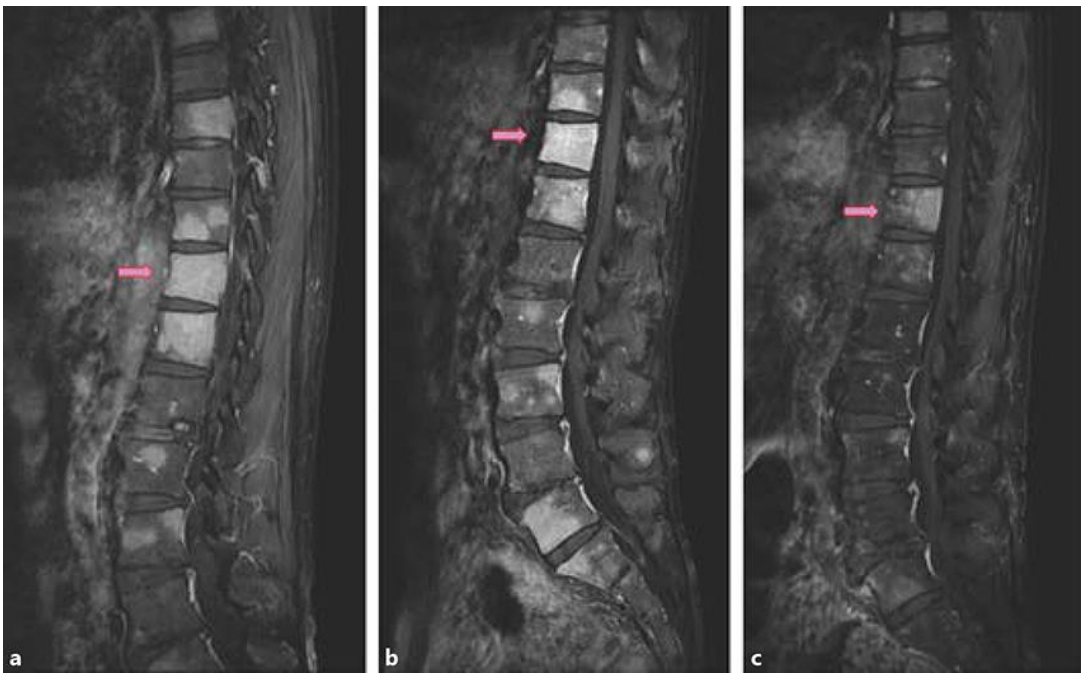

Fig. 3. Magnetic resonance imaging at initial diagnosis (**a**), at after 6 cycles of modified THP-COP (cyclophosphamide 1,200 mg [90%], pirarubicin 80 mg [90%], prednisolone 60 mg day 1–5) treatment (**b**), and at 9 months after the initiation of pralatrexate treatment (**c**). Asterisks indicate Th 11.