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CONCISE COMMUNICATION

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Pralatrexate for refractory mycosis fungoides in two Japanese patients

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Abstract

Pralatrexate has been approved for the treatment of relapsed/refractory peripheral T cell lymphomas. Studies in the U.S. also support the clinical efficacy of pralatrexate to treat advanced-stage cutaneous T-cell lymphomas, but outcomes in Japanese patients have not yet been reported. We herein describe two Japanese patients with heavily-pretreated relapsed/refractory mycosis fungoides that were successfully controlled by pralatrexate.

KEYWORDS
chemotherapy, cutaneous T-cell lymphoma, pralatrexate, refractory mycosis fungoides

1 | INTRODUCTION

Mycosis fungoides (MF) is the most prevalent form of cutaneous T-cell lymphoma (CTCL).[1] Advanced-stage MF has a poor prognosis[2] and requires systemic therapies.[1] Pralatrexate, a folic acid analog metabolic inhibitor, has been approved in the U.S.A. since 2009 for the treatment of relapsed/refractory peripheral T-cell lymphoma (PTCL), but was launched in Japan in 2017.[3] In patients with advanced-stage CTCL, U.S. studies with pralatrexate showed clinical response rates up to 58%,[4,5] but outcomes in Japanese patients have not yet been reported. We describe the clinical outcomes of two Japanese patients with relapsed/refractory MF who were treated with pralatrexate.

2 | CASE REPORT

2.1 | Case 1

A 58-year-old Japanese man was diagnosed with MF 6 years ago, and was classified as stage IIB (T3N0M0B0)[6] 3 years later. Although some erythema and tumors were resolved with mogamulizumab (1 mg/kg/week, 8 cycles), new tumors appeared after the treatment ended. Histopathological findings revealed $CD30^+$ large-cell transformation, and brentuximab vedotin (BV; 1.8 mg/kg/3 weeks, 8 cycles) was started. After three cycles of BV, the tumors reduced but the erythema remained. Subsequent courses of therapy included vorinostat (400 mg/day), which led to drug-induced liver injury, oral bexarotene (225 mg/day), a second course of BV (1.8 mg/kg/3 weeks, 8 cycles) and mogamulizumab (1 mg/kg/week, 5 cycles), each providing an inadequate response. A third course of BV (2 cycles) with ionizing radiation therapy (36 Gy, left cheek tumor), which resulted in drug eruption, oral etoposide monotherapy (50 mg/day) and interferon-gamma (2 million IU, 7 doses), followed but none of those led to an adequate response. Treatment with ionizing radiation (34 Gy, right cheek) with etoposide (25 mg/day) combined with sobuzoxane (400 mg/day) partially reduced his erythema and lesions, but new tumors appeared that required further ionizing radiation therapy (34 Gy, left hand).

He then began intravenous treatment with pralatrexate (30 mg/m^2 once weekly for 6 weeks in 7-week cycles). He also received a mucositis prophylactic regimen of intramuscular vitamin B12 (0.5 mg every 4 weeks), oral folic acid (1.25 mg daily),

oral cryotherapy prior to and for 30 minutes after pralatrexate, and dental care provided by a dentist. Before and after three cycles of pralatrexate treatment, the modified severity weighted assessment tool (mSWAT) score improved from 53.5 to 31.5 and the soluble IL-2 receptor value decreased from 4,608 U/mL to 2,731 U/mL. Adverse reactions included mild anemia (hemoglobin 11.7 g/dL), nausea and some mucositis lesions, but none of them were particularly severe. However, his treatment was changed from pralatrexate to oral forodesine due to general fatigue. At 2.5 months after the discontinuation of pralatrexate, his mSWAT score worsened to 69.7 (Figure 1). He resumed pralatrexate treatment and radiation therapy, and after two cycles of treatment, most of the tumors and erythema disappeared. He had a partial response for 5 months, but then the erythema and plaques flared up (mSWAT score, 34), and he changed to BV therapy.

2.2 | Case 2

A 60-year-old Japanese man was diagnosed with MF 14 years ago, and was classified as stage IIB (T3N0M0B0)[6] 7 years later. Previous therapies included interferon-gamma (1 million IU, 2 doses), etoposide (50 mg/day), methotrexate (10 mg/week) and oral prednisone (approximately 20 mg/day), but he had inadequate responses to all of them. Although vorinostat (400 mg/day) reduced some of the erythema and plaques, it led to anorexia and general fatigue. His atypical lymphocytes were positive for CCR4, and treatment with mogamulizumab (1 mg/kg/week, 8 cycles) was initiated. Mogamulizumab led to partial remission for 10 months, but new tumors gradually developed on his legs. A skin biopsy revealed $CD30^+$ large-cell transformation. BV (1.8 mg/kg/3 weeks, 4 cycles) led to normalization of soluble IL-2 receptor levels and some tumors disappeared, but the tumor on his buttocks remained and required ionizing radiation

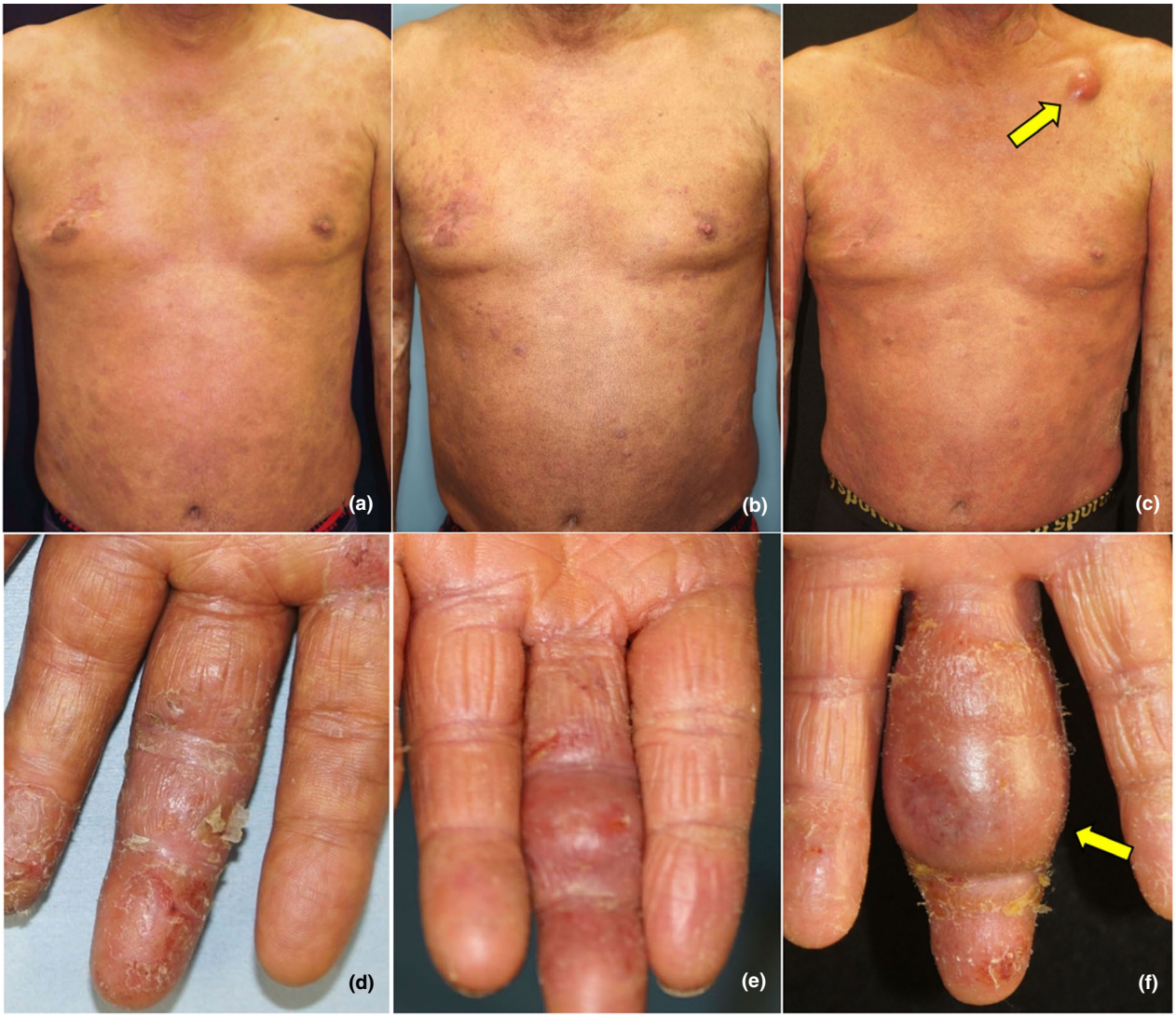

FIGURE 1 Response to pralatrexate in patient 1. (a, d) Before treatment with pralatrexate. (b, e) After three cycles of treatment with pralatrexate. (c, f) At 2.5 months after the discontinuation of pralatrexate. Most erythema had resolved with pralatrexate, but after discontinuation, erythema flare-ups and rapid tumor formation/enlargement were observed (arrows) [Color figure can be viewed at wileyonlinelibrary.com]

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therapy (36 Gy). Sobuzoxane (400 mg/day) and etoposide (25 mg/day) led to a partial reduction of the tumors but did not suppress new tumor formation.

He began treatment with intravenous pralatrexate (30 mg/m^2 once weekly for 6 weeks in 7-week cycles) together with the same mucositis prophylaxis as described for Case 1. After two cycles of treatment, the erythema, which was recalcitrant to previous therapies, resolved and the mSWAT score decreased from 49.2 to 17.5 (Figure 2). Although the tumor on his left foot remained, no new tumors emerged, and a partial response was maintained for 15 months with continued pralatrexate therapy. The patient experienced mild nausea and general fatigue, but mucositis and severe adverse events were not observed. 16 months later, some erythema and plaques appeared on his trunk and extremities. Bexarotene (300 mg/day) was added at 17 months, but erythema and tumors became more frequent rapidly and mSWAT worsened to 87. At present, he has been changed to gemcitabine therapy.

3 | DISCUSSION/CONCLUSION

In Japan, about 90% of malignant lymphomas involving the skin are CTCLs, with MF being the most prevalent.[1] Although most patients with MF present with early-stage disease, about one-third of them experience disease progression, and 26% of them die due to MF.[2] Patients with advanced stages have a poor prognosis, with a median survival of 3.4 (stage III) to 4.7 years (stage IIB).[2]

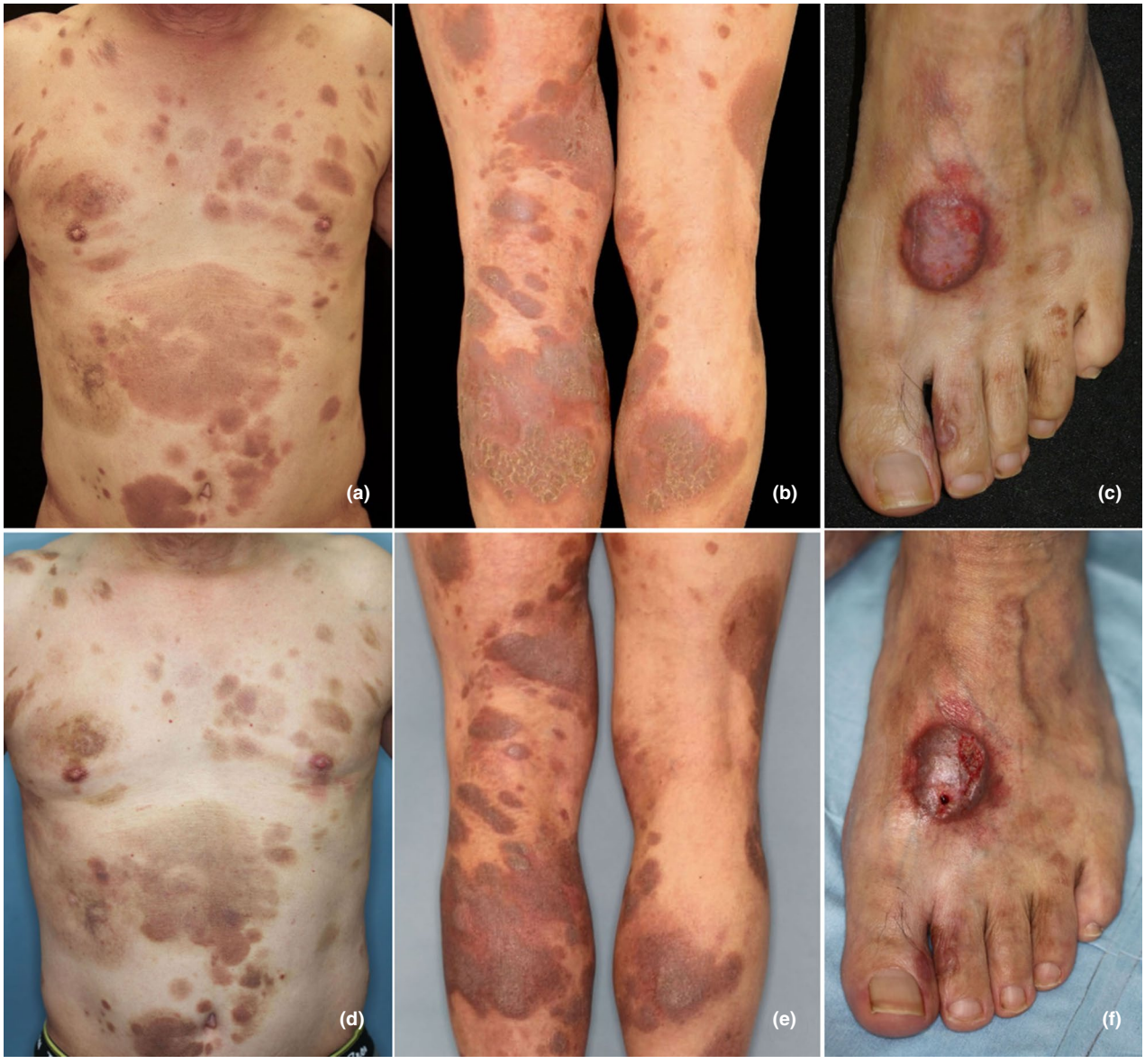

FIGURE 2 Response to pralatrexate in patient 2. (a–c) Before beginning treatment with pralatrexate. (d–f) After two cycles of treatment with pralatrexate [Color figure can be viewed at wileyonlinelibrary.com]

The chronic and recurrent nature of MF progression necessitates repeated systemic treatment for disease control. Although various treatment options exist, comparative trials and evidence-based treatment algorithms to guide treatment prioritization have not yet been established.[7]

Pralatrexate is a folate analog metabolic inhibitor that blocks dihydrofolate reductase, thereby preventing thymidylate and purine synthesis, which results in cell cycle arrest in the S phase.[8] Pralatrexate has a higher affinity for reduced folate carrier type 1 (RFC-1) compared to MTX, and therefore it is preferentially taken up by many tumor cells that overexpress RFC-1 and has a markedly greater activity than MTX.[8,9] Pralatrexate has been approved for relapsed/refractory PTCL in the U.S. (2009) based on results from a PROPEL study.[10] Pralatrexate was subsequently approved in Japan (in 2017) for treating relapsed/refractory PTCL after a phase I/II study in Japan demonstrated its efficacy and tolerability.[11] In the PROPEL study, pralatrexate (30 mg/m^2/week intravenously for 6 weeks in 7-week cycles) had a response rate of 58% in 12 patients with transformed MF.[4] Subsequently, in a prospective dose-finding study in heavily-pretreated U.S. patients, including relapsed/refractory MF, pralatrexate (15 mg/m^2/week for 3 of 4 weeks) resulted in a 45% response rate after a median of four cycles.[12] The most common treatment-related adverse events were mucosal inflammation (48%), fatigue (38%) and nausea (31%).[12] Foss et al. reported a study of 27 U.S. patients with relapsed/refractory MF or Sézary syndrome treated with pralatrexate (10 to 30 mg/m^2 weekly for 3 of 4 weeks, or every other week) and partial or complete clinical responses were observed in 57% of patients.[5] These results suggest that pralatrexate has a clinical efficacy and confirms a high overall response rate at doses even less than 15 mg/m^2 in the treatment of advanced CTCL. In addition, pralatrexate has been investigated in combination with bexarotene[13,14] and romidepsin.[15] These combination therapies have been reported to have high overall response rates of more than 50%, and can be efficient and well-tolerated treatments for advanced-stage MF.

Although some preceding therapies provided temporary partial remission, our patients experienced relapses. We used pralatrexate at a dose of 30 mg/m^2/week for 6 weeks in 7-week cycles, which is the approved regimen for relapsed/refractory PTCL based on clinical trials.[10,11] Pralatrexate suppressed new tumor formation within two to three cycles of treatment and led to a partial response. As adverse events, mucositis was controlled by prophylactic measures, but moderate general fatigue and nausea were observed, so that treatment was temporarily discontinued in Case 1. If intolerable side effects with pralatrexate are encountered, a lower-dose regimen should be considered.[5,12] In Case 2, the patient experienced a long-term partial response and then relapsed, but the patient did not want to change to another therapy or combination therapy with other drugs, resulting in a rapid progression. It may be reasonable to combine pralatrexate with other agents or treatment modalities if the disease has progressed.[7]

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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