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RESEARCH ARTICLE

A novel mouse model of cutaneous T-cell lymphoma revealed the combined effect of mogamulizumab with psoralen and ultraviolet a therapy

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Abstract

Mycosis fungoides (MF) is a subtype of cutaneous T-cell lymphoma (CTCL). Topical or systemic treatment with psoralen, such as 8-methoxypsoralen (8-MOP), followed by ultraviolet A (UVA) irradiation (PUVA therapy) is an effective phototherapy for early-stage MF. However, the efficacy of PUVA therapy for advanced-stage MF is not satisfactory, and the ideal combination partner for PUVA therapy has not yet been found. In this study, we developed a new mouse model of CTCL in which efficacy of PUVA was detected and further evaluated the efficacy of combination treatment of PUVA and mogamulizumab, an anti-CCR4 monoclonal antibody. Cytotoxicity of PUVA therapy against HH cells, a CTCL cell line, was observed in vitro. The cytotoxicity was dependent on both 8-MOP and UVA. Using HH cells, we developed a mouse model in which HH cells were subcutaneously inoculated in the ear. In this model, PUVA therapy suppressed tumour growth with statistical significance, while 8-MOP or UVA alone did not. Combination therapy of PUVA and mogamulizumab showed greater antitumor activity than either monotherapy with statistical significance. In the histological analysis of the tumour tissue, PUVA accelerated tumour necrosis and then induced the infiltration inflammatory cells in the necrotic area, suggesting that these cells served as effector cells for mogamulizumab. This combination therapy is expected to be a beneficial option for CTCL therapy.

KEYWORDS
cutaneous T-cell lymphoma, mogamulizumab, mycosis fungoides, PUVA therapy, xenograft model

1 | INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a subtype of primary cutaneous lymphoma. Most CTCL patients are categorized into two subtypes: mycosis fungoides (MF) and Sezary syndrome (SS); all other patients are diagnosed with various minor subtypes. MF induces patches and plaques on the surface of skin in the early stage (IA-IIA). Most patients show a favourable prognosis and clinical remission. However, some develop relapse and progress to the advanced stage. In the advanced stage (IIB-IV), cutaneous tumours spread to lymph node and other organs.[1] Patients with advanced-stage MF sometimes show resistance to current therapies and have a poor prognosis.[2] Therefore, novel

effective therapies are still required to prolong clinical remission in the early stage and improve therapeutic efficacy in the advanced stage.

Skin-directed therapy is the first-line treatment for the patients with skin-limited lesions. When the disease is refractory to multiple skin-directed therapies or spreads to the deep skin tissue and other organs, patients are treated with a combination of skin-directed therapies and systemic therapies, such as psoralen and ultraviolet A (PUVA) therapy and interferon α.[1] SS is an advanced leukaemic subtype of CTCL with atypical abnormal T cells in the erythema and blood. SS patients are usually treated with a combination of skin-directed therapies and systemic therapies as advanced-stage MF.

PUVA therapy is a common phototherapy for CTCL with patches and plaques. 8-methoxypsoralen (8-MOP), a psoralen derivative, is orally or topically administered, and patients are then irradiated with UVA. 8-MOP activated by UVA intercalates into DNA double strands, leading to cell death.[3] Although early-stage CTCL patients treated with PUVA show a good prognosis, this approach is not sufficiently effective for tumours in the deep skin tissue and other organs in the advanced stage.[4]

Mogamulizumab is a monoclonal antibody against CC chemokine receptor 4 (CCR4) with enhanced antibody-dependent cellular cytotoxicity (ADCC) by POTELLIGENT® technology.[5] It was approved in Japan for the treatment of MF and SS in 2014, followed by Europe and the United States in 2018. The progression-free survival (PFS) of advanced-stage CTCL patients treated with mogamulizumab monotherapy was superior to that of patients treated with vorinostat, the current standard of care in the United States,[1] according to a phase 3 study.[6] Thus, combination therapy of mogamulizumab with other drugs is expected to have promising therapeutic activity. However, the optimal immunosuppressive chemotherapy must be selected in order to maximize the efficacy, since NK cells that could be reduced by chemotherapy are essential effector cells for ADCC activity of mogamulizumab. Skin-directed therapy without any immunosuppressive effects, such as PUVA, thus has the potential to be more suitable.

No previous studies have evaluated the antitumor effect of PUVA against CTCL using a nonclinical animal model. Although several combination therapies with PUVA have been tested in the clinical setting, the efficacy is not satisfactory.[7] One reason for the lack of any effective combination therapies is thought to be a lack of animal models in which the efficacy of PUVA can be appropriately evaluated.

The present study established the first mouse model of CTCL in which efficacy of PUVA was detected, and we investigated the effect of combination therapy of mogamulizumab with PUVA.

2 | METHODS

2.1 | Cells and reagents

HH, a human CTCL cell line expressing CCR4,[8,9] was obtained from American Type Culture Collection. The cells were cultured in RPMI1640 medium (Thermo Fisher Scientific) supplemented with 10 vol% heat-inactivated fetal bovine serum (Thermo Fisher Scientific).

Mogamulizumab was obtained from Kyowa Kirin Co., Ltd. 8-MOP (Oxoralen tab.) was obtained from Taisho Pharmaceutical Holdings.

2.2 | Cytotoxicity of PUVA

HH cells were seeded in 96-well flat plate (1×10^4 cells/well) and cultured for 24 h at 37°C in 5 vol% CO_2 condition. 8-MOP was added to each well, and the cells were incubated for 2 h at 37°C in 5 vol% CO_2 condition. Culture medium was replaced with phosphate-buffered saline (PBS), and the cells were irradiated with 1, 2 or 5 J/cm^2 of UVA using Solar Simulator SOL500 (Dr. Hönle). PBS was then replaced with medium, and the cells were cultured for 72 h at 37°C in 5 vol% CO_2. WST-8 reagent (Dojindo Laboratories) was added to each well, and the absorbance at 450 nm was measured.

The viability of HH was calculated as follows:

$$\text{Viability}\,(\%) = \frac{(\text{Mean value of samples treated with PUVA})}{(\text{Mean value of untreated samples (without } 8-\text{MOP in the absence of UVA}))} \times 100.$$

$$\text{Relative viability}\,(\%) = \frac{(\text{Mean value of samples treated with PUVA})}{(\text{Mean value of samples treated only with UVA})} \times 100$$

2.3 | Animals

Five-week-old male BALB/cAJcl-nu/nu mice were purchased from Clea Japan and maintained in individually ventilated caging system with free access to solid diet (CL-2; Clea Japan) and tap water. The animal facility was kept at 20 to 26°C and a relative humidity of 30% to 70% with a 12-h light–dark cycle.

This study was approved by the Institutional Animal Care and Use Committee and was performed in accordance with the animal welfare rules of Kyowa Kirin, Fuji Research Park, which is accredited by AAALAC International.

2.4 | Antitumor activity of UVA and 8-MOP monotherapy

HH cells suspended in PBS containing 50 vol% Matrigel Matrix basement membrane (Corning) were subcutaneously inoculated in the ear of 60 mice (2×10^7 cells/0.1 ml/head). Seven days after the inoculation, 45 mice were divided into 3 groups (control, 8-MOP and UVA groups) so that the mean and standard deviation (SD) of the

tumour volume and body weight were comparable among groups. The day of grouping was designated as Day 0.

On Day 1, 100 mg/kg of 8-MOP suspended in 5% methylcellulose was orally administered to mice in the 8-MOP group. The mice were kept in the dark for approximately 2 h. No administration was conducted for the control or UVA group. All mice were then anaesthetised. In the UVA group, the whole body of the mice was wrapped with aluminium foil except for the tumour region in the ear and exposed to UVA at 5 J/cm^2 (maximum dose in the cytotoxicity study described above) using a Solar Simulator SOL500. The tumour diameter and body weight were measured on Days 7 and 14. The tumour volume was calculated as follows:

Tumour volume (mm^3) = l×w^2×0.5 (l: length; w: width)

2.5 | Antitumor activity of mogamulizumab in combination with PUVA

HH cells were inoculated in the ear of 100 mice. Seven days after the inoculation, 60 mice were divided into 4 groups (control, mogamulizumab, PUVA and their combination groups). Inoculation and grouping were conducted in the same way as described above.

On Days 1 and 8, mogamulizumab (20 mg/kg) was intravenously administered. On Day 1, 8-MOP (100 mg/kg) was orally administered to mice in the PUVA and combination groups. Mice were kept in the dark for approximately 2 h. All mice were anaesthetised, and the mice in the PUVA and combination groups were irradiated with UVA in the same manner as described above. The tumour diameter and body weight were measured on Days 7 and 14.

Statistical analyses were conducted using the JMP15 software program (SAS Institute). Differences in the tumour volume on Day 14 between the control and each treatment group were assessed by Dunnet's test. When the tumour volumes in both the mogamulizumab and PUVA groups were significantly smaller than in the control group, the differences in the tumour volume between the combination group and each monotherapy group were assessed by Dunnet's test. When the tumour volume in the combination group was significantly smaller than in either the mogamulizumab or PUVA group, the combination of mogamulizumab and PUVA was considered to exert superior antitumor activity to either monotherapy.

p-values <0.05 were considered statistically significant.

2.6 | Histological analyses of tumour tissues

The 12 mice excluded from the antitumor study were divided into 4 groups (control, mogamulizumab, PUVA and their combination groups) and treated with mogamulizumab and PUVA the day after grouping. Grouping and treatment were conducted in the same way as described above. Approximately 24 h after treatment, mice were euthanized, and the tumour tissues were collected and stored in 10% formalin neutral buffered solution.

Samples were embedded in paraffin and sectioned. One section was stained with haematoxylin and eosin (H&E) by a standard procedure, and the other two sections were stained with monkey-absorbed anti-human IgG heavy and light chain antibody (Bethyl Laboratories) or anti-mouse F4/80 antibody (BioLegend) as the primary antibody, followed by staining with anti-goat IgG or anti-rat IgG as the secondary antibody, respectively, and 3,3′-diaminobenzidine (DAB). The sections were examined microscopically to observe any morphological changes or the distribution of mogamulizumab and F/80-positive monocytes and macrophages.

3 | RESULTS

3.1 | Cytotoxicity of PUVA

The viability of HH cells treated with 8-MOP and UVA is shown in Figure 1. Without UVA, 8-MOP showed only slight cytotoxicity against HH cells up to 100 μmol/L and showed clear cytotoxicity at 500 μmol/L. As shown in Figure 1A, the viability of HH cells treated with PUVA (combination of 8-MOP and UVA) was decreased in an 8-MOP concentration-dependent manner and was lower than that of cells treated with only 8-MOP. Viability was recalculated using the viability of HH cells treated with each dose of UVA alone as "100% viable" (relative viability, Figure 1B). The line graph of relative viability of HH cells was left-shifted with increasing dose of UVA, meaning that UVA enhanced the cytotoxicity of 8-MOP.

3.2 | Establishment of a mouse CTCL model to evaluate the antitumor activity of PUVA

The antitumor activity of 8-MOP or UVA was examined using mice subcutaneously inoculated with HH cells in the ear. Tumour volumes in the 8-MOP and UVA groups were increased similarly to those in the control group (Figure 2A). In contrast, as shown in Figure 2B, the tumour growth in the PUVA group was suppressed compared to that in the control group ($p = 0.0061$), and the mean tumour volume in the PUVA group was significantly smaller than that in the control group on Day 14 ($p = 0.0061$).

3.3 | Combination therapy of PUVA and mogamulizumab

The antitumor activity of PUVA, mogamulizumab and their combination was examined (Figure 2B). The mean tumour volume in both the PUVA and mogamulizumab groups was smaller than that in the control group on Day 14 with statistical significance ($p = 0.0061$ and

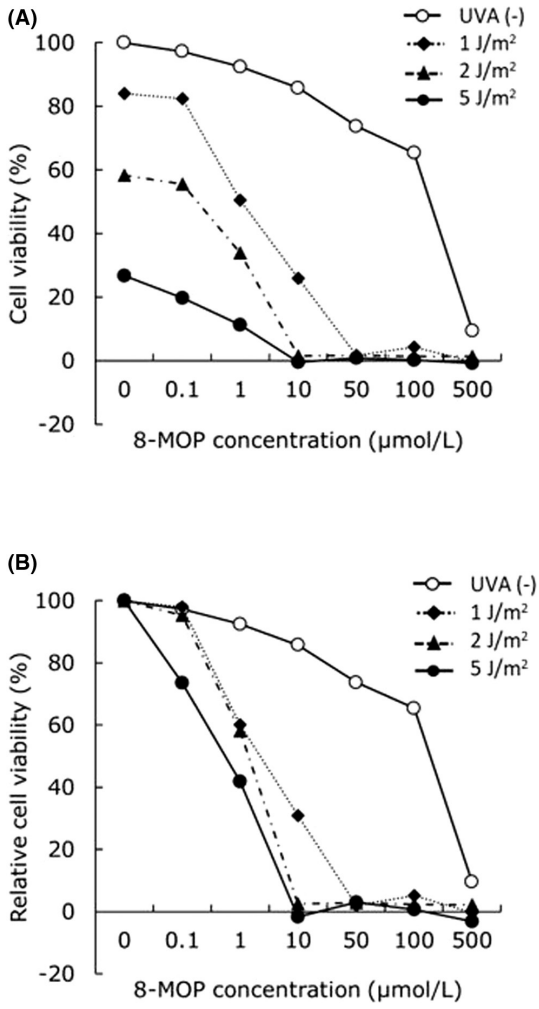

FIGURE 1 Viability of HH cells treated with 8-MOP and UVA in vitro. HH cells were treated with 8-MOP and irradiated with 1, 2 or 5 J/cm^2 of UVA. After incubation for 72 h, the absorbance at 450 nm was measured, and the viability was calculated. Samples without treatment of 8-MOP in the absence (A) or presence (B) of each dose of UVA irradiation were regarded as 100% viable. Each plot represents the mean results of triplicate.

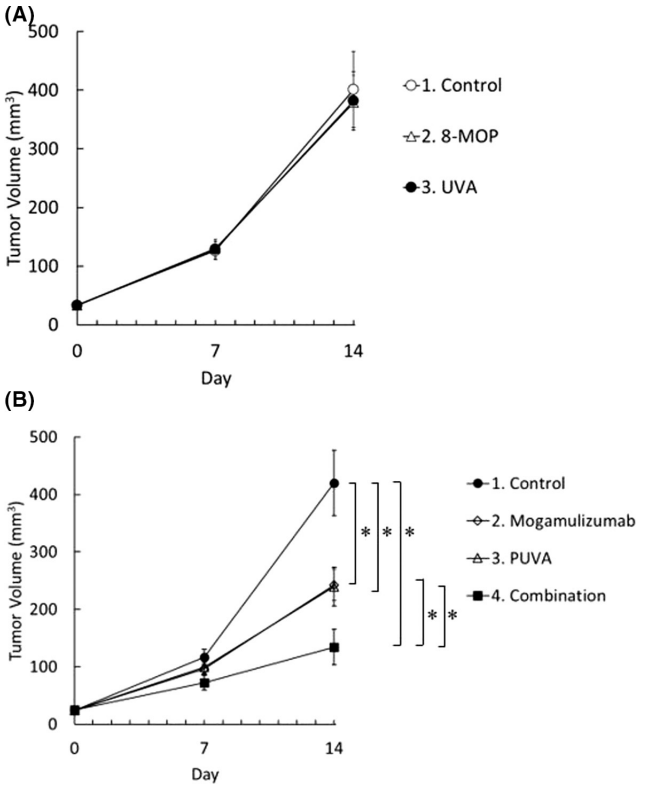

FIGURE 2 Tumour growth in a nude mouse model with HH cells subcutaneously inoculated in the ear. Nude mice ($n = 15$/group) were inoculated with HH cells in subcutaneous tissue in the ear. On Day 1, 100 mg/kg of 8-MOP administration and 5 J/m^2 of UVA irradiation were performed (A, B), and 20 mg/kg of mogamulizumab was administered on Days 1 and 7 (B). Two mice in the UVA group (A) and one in the PUVA group (B) died on Day 1. Each plot represents the mean ± SE.*$p < 0.05$.

0.0062, respectively). The mean tumour volume in the combination group was significantly smaller than that in the mogamulizumab and PUVA groups on Day 14 ($p = 0.030$ and 0.040, respectively).

3.4 | Results of histological analyses

Histopathology images of tumour tissues stained by H&E are shown in Figure 3A,C. Tumour tissues consisted of tumour cells, and mitosis was frequently found. A pale-coloured necrotic area was found in the tumour tissues of most animals, and the necrotic areas in the tumour in the PUVA and combination groups were wider than those in the control and mogamulizumab groups. Cell debris and infiltrated inflammatory cells were diffusely found in the area, which are typical characteristics of necrosis. The degree of necrosis was similar between the PUVA and combination groups.

Immunohistochemical images of tumour tissues stained by anti-human IgG are shown in Figure 3B,D. Positive human IgG staining, indicating the distribution of mogamulizumab, was found diffusely in tumours treated with mogamulizumab and combination therapy. The degree of staining in the non-necrotic area was similar between the mogamulizumab and combination groups. The staining in the necrotic area appeared to be stronger than that in the non-necrotic area.

Immunohistochemical images of the tumour tissues stained by anti-F4/80 antibody are shown in Figures 3E. F4/80-positive cells were distributed diffusely in the non-necrotic area in all groups. These cells were observed more frequently in the necrotic area than in the surrounding non-necrotic area.

4 | DISCUSSION

A lack of an appropriate preclinical mouse model to evaluate PUVA therapy has led to difficulties examining combinations with other therapies for CTCL. To overcome this problem, we developed a new mouse model of CTCL to determine the efficacy of PUVA.

First, we found that HH cells responded to PUVA treatment in vitro, indicating that they were appropriate for evaluating the

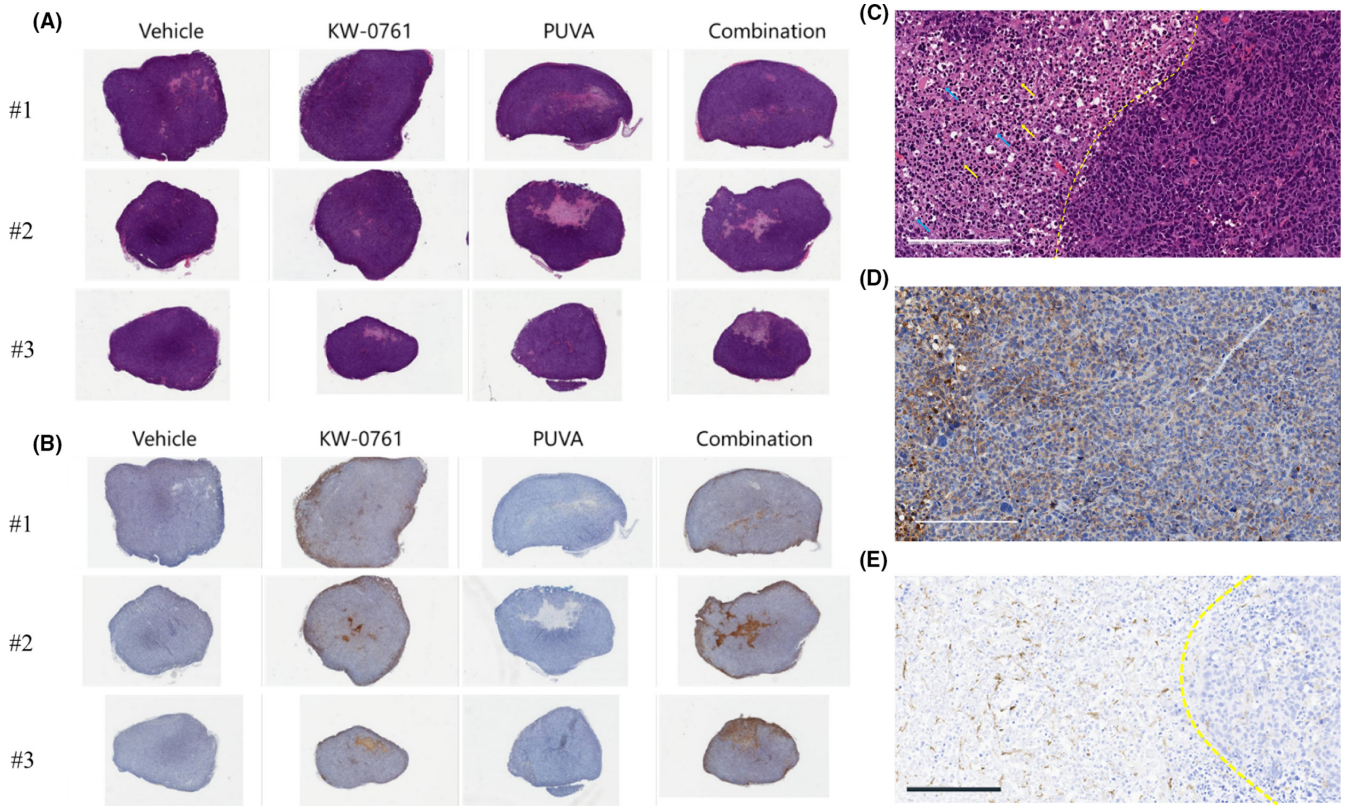

FIGURE 3 Results of a histological analysis of tumour tissue treated with PUVA and mogamulizumab. Nude mice with tumours in the ear were treated with PUVA and mogamulizumab ($n = 3$/group), and tumour tissues were collected 24 h after the treatment. Sections of tumour tissues were stained with H&E (A and C), anti-human IgG antibody (B and D) and anti-mouse F4/80 (E). Individual (A and B) and representative (C, D and E, combination group) results are shown. (C) The necrotic region can be seen in the left half of this image. Cell debris (blue arrows) and infiltrated inflammatory cells (yellow arrows) were diffusely found in the necrotic area. (D) Positive human IgG staining in the non-necrotic area. (E) mouse F4/80-positive cells in the necrotic area (left half of the image) observed more frequently than that in the surrounding non-necrotic area. Scale bar: 200 μm.

cytotoxicity of PUVA. The viability of HH cells treated with PUVA decreased in an 8-MOP concentration-dependent manner. Since the viability of HH cells treated with only UVA without 8-MOP also decreased in a UVA dose-dependent manner, the viability was recalculated as the relative viability in order to distinguish cytotoxicity due to PUVA from that due to UVA alone. The relative viability of HH cells treated with 8-MOP decreased with increasing dose of UVA, indicating that the cytotoxicity of 8-MOP was enhanced by UVA.

Next, we performed animal experiments using HH cells. Although PUVA treatment showed cytotoxicity against HH cells in vitro, we were unlikely to observe antitumor activity of PUVA using a conventional model in which a tumour was subcutaneously inoculated into the flank, as UVA does not sufficiently penetrate subcutaneous tissue. Since we expected UVA to reach the tumour tissue when inoculated into thin skin with little subcutaneous tissue, we developed a mouse model with a tumour subcutaneously inoculated in the ear. In our mouse model, neither 8-MOP nor UVA alone showed antitumour activity. However, PUVA suppressed tumour growth with statistical significance. These results clearly showed that we successfully established an appropriate animal model of CTCL for evaluating the efficacy of PUVA. UVA monotherapy did not suppress tumour growth, although the same dose of UVA (5 J/m^2) without 8-MOP decreased the viability of HH cells in the cell viability assay in vitro. It was likely that UVA was attenuated through the skin in vivo, while HH cells were directly exposed to UVA in vitro.

We investigated the antitumor activity of combination therapy of mogamulizumab and PUVA using this model. Both mogamulizumab monotherapy and PUVA monotherapy significantly suppressed the tumour growth compared to control. Combination of mogamulizumab and PUVA greatly suppressed the tumour growth compared to either monotherapy with statistical significance. In the histological analysis of tumour tissue, mogamulizumab seemed to distribute more abundantly in the necrotic area than the non-necrotic area, possibly because in the necrotic area, the tissue structure was destroyed, which otherwise would prevent macromolecule infiltration into the tissue.[10] PUVA accelerated tumour necrosis and enhanced the infiltration of many inflammatory cells in the necrotic area. The result of immunohistochemistry of F4/80 revealed abundant monocytes and macrophages in the necrotic area adjacent to the non-necrotic area in the tumour tissue, suggesting that most of the infiltrated inflammatory cells were monocytes and macrophages. Since only a few cells were found in the centre of the necrotic area, the quantitative comparison of the number of F4/80-positive cells in the entire necrotic area among groups was not possible. However,

PUVA is expected to have increased the number of macrophages and monocytes in tumour tissue as a whole with the expansion of necrotic area. Furthermore, mouse FcγRIV expressed on monocytes and macrophages mainly contributes to the antitumor effect of defucosylated human IgG in mouse model.[11] Therefore, it is likely that the increased monocytes and macrophages in the necrotic area by PUVA enhanced the cytotoxicity of mogamulizumab.

CCR4 is expressed on not only CTCL cells but also normal T cells such as regulatory T cells (Treg). The depletion of Treg is considered to be one of the most important immuno-oncological approaches.[12] Our model has the defect in the contexture; the effect of mogamulizumab could not be evaluated because we used nude mice. However, because the primary mechanism of action of mogamulizumab is the direct killing of cancer cells by ADCC, the antitumor activity of mogamulizumab in this model is expected to be relevant to the efficacy in CTCL patients.

Whether side effects of mogamulizumab, such as skin rash,[13] are augmented or ameliorated by combination with PUVA is unclear. Given that one of the side effects of PUVA is dermatosis,[14] this combination may exacerbate skin disorders. However, since PUVA can reduce skin graft-versus-host disease,[15] the combination may ameliorate mogamulizumab-induced skin rash. Careful attention should be paid when clinical application is considered.

5 | CONCLUSION

To our knowledge, this is the first report describing the establishment of a CTCL mouse model in which the efficacy of PUVA was able to be evaluated. In addition, the present results indicated that combination of mogamulizumab and PUVA was superior to either monotherapy alone with regard to efficacy. This combination therapy is expected to be a beneficial option for CTCL therapy.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final manuscript. Keiko Nakahashi: Conceptualization, Methodology, Formal analysis, Writing–Original Draft, Visualization. Kaito Nihira: Methodology, Formal analysis, Investigation, Writing–Review & Editing. Miyoko Suzuki: Methodology, Validation, Formal analysis, Investigation. Toshihiko Ishii: Writing–Review & Editing, Project administration. Kazuhiro Masuda: Writing–Review & Editing, Project administration. Kiyotoshi Mori: Writing–Review & Editing, Supervision.

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CONFLICTS OF INTEREST

All the authors are employed by Kyowa Kirin Co., Ltd.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Mehta-Shah N, Horwitz SM, Ansell S, et al. NCCN guidelines insights primary cutaneous lymphomas, version 2.2020. *J Natl Compr Canc Net*. 2020;18(5):522-536.
2. Whittaler S, Hoppe R, Prince HM. How i treat mycosis fungoides and Sézary syndrome. *Blood*. 2016;127(25):3142-3153.
3. Bethea D, Fullmer B, Syed S, et al. Psoralen photobiology and photochemotherapy: 50 years of science and medicine. *J Dermatol Sci*. 1999;19(2):78-88.
4. Olsen EA, Hodak E, Anderson T, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: a concensus statement of the united stated cutaneous lymphoma consortium. *J Am Acad Darmatol*. 2016;74(1):27-58.
5. Ishii T, Ishida T, Utsunomiya A, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. *Clin Cancer Res*. 2010;16(5):1520-1532.
6. Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19(9):1192-1204.
7. Humme D, Nast A, Erdmann R, Vandersee S, Beyer M. Systematic review of combination therapies for mycosis fungoides. *Cancer Treat Rev*. 2014;40:927-933.
8. Starkebaum G, Loughran TP Jr, Waters CA, Ruscetti FW. Establishment of an IL-2 independent, human T-cell line possessing only the p70 IL-2 receptor. *Int J Cancer*. 1991;49(2):246-253.
9. Kamijo H, Sugaya M, Takahashi N, et al. BET bromodomain inhibitor JQ1 decreases CD30 and CCR4 expression and proliferation of cutaneous T-cell lymphoma cell lines. *Arch Dermatol Res*. 2017;309:491-497.
10. Jain RK. Physiological barriers to delivery of monoclonal antibodies and other macromolecules in tumors. *Cancer Res*. 1990;50(3 Suppl):814-819.
11. Braster R, Bögels M, Benonisson H, et al. A fucosylated IgG targets FcRIV for enhanced tumor therapy in mice. *Cancer*. 2021;13(10):2372-2390.
12. Ni X, Langridge T, Duvic M. Depletion of regulatory T cells by targeting CC chemokine receptor type 4 with mogamulizumab. *Onco Targets Ther*. 2015;4(7):e1011524-1-2.
13. Wang JY, Kelsey H, Neal TM, et al. Histopathologic characterization of mogamulizumab-associated rash. *Am J Surg Pathol*. 2020;44(12):1666-1676.
14. Elma DB, Seth RS. Phototherapy for cutaneous T-cell lymphoma. *Dermatol Ther*. 2003;16:303-310.
15. Furlong T, Leisenring W, Storb R, et al. Psoralen and ultraviolet a irradiation (PUVA) as therapy for steroid-resistant cutaneous acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8(4):206-212.

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