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ORIGINAL RESEARCH

Comparison of the Efficacy and Safety of Bexarotene and Photo(Chemo)Therapy Combination Therapy and Bexarotene Monotherapy for Cutaneous T-Cell Lymphoma

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ABSTRACT

Introduction: Cutaneous T-cell lymphoma (CTCL) is a chronic condition with low malignancy. The combined use of therapeutic agents and photo(chemo)therapy is widely applied for the treatment of CTCL. The efficacy and safety of bexarotene and photo(chemo)therapy combination therapy were previously confirmed in Japanese patients with CTCL. The efficacy and safety of the bexarotene and photo(chemo)therapy combination therapy was compared with bexarotene monotherapy in Japanese patients with CTCL.

Methods: This was a randomized, open-label, two-parallel-group, active-control specified clinical study in Japanese patients diagnosed with CTCL carried out over 8 weeks with a study extension conducted at two institutions. This study was registered in Japan Registry of Clinical Trials (jRCTs041180094).

Results: In the combination therapy group, 22 subjects received oral bexarotene (300 mg/m^2 body surface area) once daily, followed by bath-psoralen and ultraviolet (UV) A or narrowband UVB. In the monotherapy group, 24 subjects received oral bexarotene (300 mg/m^2) once daily. The efficacy analysis using the modified Severity-Weighted Assessment Tool, which included 39 patients, showed a response rate of 81.0% (17/21) in the combination therapy group and 83.3% (15/18) in the monotherapy group. No statistically significant difference was detected between groups. In the combination therapy group, four subjects showed a complete clinical response or complete response, and subjects with a partial response exhibited a high rate of skin lesion resolution, significantly better than in the monotherapy group. In the safety analysis, which included 46 treated subjects (22 in the combination therapy group and 24 in the monotherapy group), no adverse events or adverse drug reactions were reported in either group.

Conclusion: Both bexarotene and photo(chemo)therapy combination therapy and bexarotene monotherapy were

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therapeutically effective in Japanese patients with CTCL and well tolerated. Combination therapy led to a higher skin lesion resolution rate and greater therapeutic effects compared with monotherapy.
Trial Registration: jRCTs041180094.

PLAIN LANGUAGE SUMMARY

This study evaluated the efficacy and safety of bexarotene monotherapy compared with bexarotene and photo(chemo)therapy combination therapy in Japanese patients with cutaneous T-cell lymphoma (CTCL). The study was a randomized, open-label, two-parallel-group, active-control specified clinical study in patients diagnosed with CTCL performed over an 8-week period with a study extension conducted in two institutions. In the combination therapy group, bexarotene (300 mg/m^2 body surface area) was administered orally once daily to 22 subjects, followed by treatment with bath-psoralen and ultraviolet A (bath-PUVA) or narrowband UVB. In the bexarotene monotherapy group, bexarotene (300 mg/m^2) was administered orally once daily to 24 subjects. Efficacy was assessed using the modified Severity-Weighted Assessment Tool. Among the 39 subjects analyzed for treatment efficacy, the response rate of the combination therapy group was 81.0% (17/21) and that of the monotherapy group was 83.3% (15/18). Differences between the two treatment groups were not statistically significant. Of the 21 subjects in the combination therapy group, 4 had a complete clinical response or complete response, and those with a partial response showed a higher skin lesion resolution rate than in the monotherapy group. The safety analysis revealed no reports of adverse events or adverse drug reactions among the 46 treated subjects (combination therapy group = 22; monotherapy group = 24). Thus, both bexarotene and photo(chemo)therapy combination therapy and bexarotene monotherapy were therapeutically effective and well tolerated in Japanese patients with CTCL. Patients receiving the combined therapy, however, showed a higher rate of skin lesion resolution.

Keywords: Bexarotene; Cutaneous T-cell lymphoma; Japanese; Phototherapy; Photochemotherapy

Key Summary Points

Why carry out this study?

Cutaneous T-cell lymphoma (CTCL) is generally treated with a combination of therapeutic agents and photo(chemo)therapy.

No studies to date have objectively compared the safety and efficacy of bexarotene monotherapy and combined bexarotene and photo(chemo)therapy in Japanese patients with CTCL.

What was learned from the study?

Bexarotene and photo(chemo)therapy combination therapy and bexarotene monotherapy are therapeutically effective in Japanese patients with CTCL and are well tolerated with no known adverse events or adverse drug reactions.

Bexarotene and photo(chemo)therapy combination therapy may induce a higher skin lesion resolution rate in Japanese patients with CTCL.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) refers to a group of extranodal non-Hodgkin's lymphomas characterized by the infiltration of malignant T-cells into the skin [1–3]. Mycosis fungoides (MF), which accounts for most CTCL, occurs mainly in middle-aged and older people with a male-to-female ratio of 9:5 [4, 5]. Most patients have an indolent clinical course lasting > 10 years, and some cases progress over years

from the patch to the plaque stage and eventually to the tumor stage. Patients whose disease state has progressed to the tumor stage develop organ infiltration and infections, leading to an extremely poor prognosis. During the disease course, the patient's quality of life markedly decreases because of the frequent occurrence or recurrence of cutaneous symptoms, which affect the patient's social life.

In recent years, international standardization of the diagnostic criteria and staging of CTCL has progressed, and treatment guidelines have been presented and disseminated in major regions of Europe and the USA by the World Health Organization and the European Organization for Research and Treatment of Cancer [6, 7]. In 2018, Ibbotson provided an invaluable perspective on the use of psoralen and ultraviolet A (UVA) therapy (PUVA) and narrowband UVB for the management of a range of skin diseases, including CTCL [8]. The Japanese clinical practice guidelines indicate treatment modalities for each stage of CTCL. Phototherapy is used as a local treatment for patients with early- (stage IA-IIA) and advanced-stage (stage IIB and worse) CTCL [9]. Of the available photo(chemo)therapy methods, PUVA and narrowband UVB therapy are mainly used. A retrospective analysis of 62 patients with CTCL treated with PUVA in Japan demonstrated the efficacy of PUVA therapy. Patients who exhibit treatment resistance, however, might have a poor prognosis [10].

Clinical trials for developing new medical entities are complicated in Japan, and thus approval for treatments that are already used in Europe and the US is often delayed. In January 2016, bexarotene, one of the most popular CTCL treatments in Europe and the US, was approved for manufacture and sale in Japan for the management of CTCL.

The reports of clinical trial on the bexarotene are based mainly on the data of patients in Europe. Therefore, because of racial differences in photosensitivity due to variations in skin color, it is essential to conduct a clinical study on the use of combination therapy in Japanese patients. The evidence supporting the efficacy and safety of combined bexarotene and photo(chemo)therapy was provided recently [11]. In that study, patients received daily oral dose of bexarotene calculated according to the body surface area (300 mg/m^2), followed by bath-PUVA or narrowband UVB. At 24 weeks after initiating treatment, the total response rate was 80.0% according to the modified Severity-Weighted Assessment Tool (mSWAT) assessment [12] and 84.0% using the Physician's Global Assessment (PGA). Response rates did not differ when stratified by disease stage. Comparison of bexarotene monotherapy with bexarotene and photo(chemo)therapy combination therapy, however, has not been reported in Japanese patients. Therefore, in the present study, the efficacy and safety were compared between bexarotene and photo(chemo)therapy combination therapy and bexarotene monotherapy in Japanese patients with CTCL.

METHODS

Study Method

This was a randomized, open-label, two-parallel-group, active-controlled specified clinical study in Japanese patients diagnosed with CTCL. This study was conducted at two sites (Nagoya City University Hospital and Osaka City University Hospital) under protocols reviewed and approved by Nagoya City University Hospital Clinical Research Review Board. In the case of multicenter specified clinical study under the Clinical Trials Act, after approval by the central Certified Review Board (CRB), the implementation permission of the administrator of each implementing medical institution has been obtained. The study conformed to the ethical principles of the Declaration of Helsinki (revised 2013) and the Clinical Trials Act in Japan. The outline of this study was registered and published in the Japan Registry of Clinical Trials (jRCT) (Trial ID; jRCTs041180094).

The major inclusion criteria were Japanese CTCL patients at least 20 years of age who provided written informed consent. The major exclusion criteria were as follows: contraindications to bexarotene use, pregnancy, breastfeeding, desire to become pregnant during the

study period, having received topical CTCL treatment within 2 weeks prior to commencing treatment, treated with UVA or UVB irradiation within 3 weeks prior to commencing treatment, treated with radiation within 4 weeks before commencing treatment, and previous treatment with bexarotene.

In the bexarotene monotherapy group, bexarotene (300 mg/m^2) was administered orally once daily after meals. Eight weeks after starting treatment, the treatment was terminated in subjects showing a partial response (PR) or better. In cases with stable disease (SD) or progressive disease (PD), photo(chemo)therapy was added, and combination treatment was performed for an additional 4 weeks. In the bexarotene and photo(chemo)therapy combination therapy group, the treatment was carried out as described previously [11]. Bexarotene (300 mg/m^2) was administered orally once a day after meals.

Irradiation Protocol for Bath-PUVA and Narrowband UVB

Bath-PUVA or narrowband UVB was performed within 4 h after oral administration of bexarotene. For bath-PUVA, irradiation was started with 0.5 J/cm^2 UVA and performed five times weekly for 4 weeks after initiating the bexarotene therapy. The irradiation dose was increased by 0.5 J/cm^2 at each irradiation session (maximum, 4.0 J/cm^2). From 4 weeks after the initiation of bexarotene therapy, if the principal investigator or co-investigator judged that there were no issues related to subject's safety and if the patient's condition appeared to have improved, the irradiation dose or the number of irradiations was changed. For narrowband UVB, treatment was started at 50–70% of the minimum erythema dose or 0.5–0.7 J/cm^2 within 4 h after oral administration of bexarotene. Irradiation was performed five times weekly for 2 weeks after the initiation of bexarotene therapy, and the irradiation dose was increased by 20% at each irradiation session (maximum, 2.0 J/cm^2). From 2 weeks after the initiation of bexarotene therapy, when the principal investigator or co-investigator judged that there were no issues related to subject's safety and if the patient's condition appeared to have improved, the irradiation dose or the number of irradiations was changed.

Efficacy Assessment

Evaluation of the efficacy and safety was performed as follows. The following items were measured or surveyed on the first day of therapy at weeks 1, 2, 3, 4, 8, 12, and 24 or the day treatment was discontinued: mSWAT, PGA, safety, blood tests, blood biochemistry, body temperature, blood pressure, pulse rate, concomitant medication and therapy, subjective symptoms, objective findings, and drug compliance status. The staging and classification of MF and Sézary syndrome were conducted as described previously [13].

The mSWAT score was interpreted as follows: clinical complete response (CCR) or complete response (CR), 100% improvement in the mSWAT score from baseline; PR 50–99% improvement; SD 25–50% improvement or 0–25% deterioration; and PD, deterioration of at least 25% or > 50% increase in the sum of the products of the greatest diameters of pathologically confirmed affected lymph nodes.

The PGA score was interpreted as follows: CCR, full resolution, no existence of the disease; PR, 50% or more improvement from baseline scores, existence of some trace of the disease or evidence of a certain degree of disease; 0–50% improvement or 25% deterioration or worse, significant remaining disease, or not significantly different from baseline; PD, 25% deterioration or worse.

Evaluations at the commencement of treatment and after 4 weeks and 8 weeks were mandatory, while evaluations at 1, 2, and 3 weeks were optional. The final evaluation was performed after 12 weeks or at the time of study termination. For the safety evaluation, information on adverse events (AEs) was collected throughout the study period.

Statistical Analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), Microsoft Office Excel 2013, and Word 2013 (Microsoft, Redmond, WA, USA). The summary statistic of the weighted data (continuous amount) was set to the number of subjects, mean value, standard deviation, minimum value, median, and maximum value unless otherwise noted. For interval data, the number of target subjects and ratios were calculated.

RESULTS

Patient Profiles

The research design and study flow chart are shown in Fig. 1. A total of 53 subjects were enrolled in 2 institutions; 7 subjects withdrew from the study, and 46 subjects received the study drug. Dynamic allocation was performed by the minimization method using the adjustment factor (facility, disease type, and disease stage); the subjects were assigned to two groups at a ratio of 1:1 (bexarotene and photo[chemo]therapy combination therapy group $n = 22$, and bexarotene monotherapy group $n = 24$). All 46 subjects were included in the safety analysis set (SAS), but 1 subject in the combination therapy group and 5 subjects in the monotherapy group were excluded from the full analysis set (FAS) because the efficacy evaluation could not be performed because of treatment discontinuation. In addition, three subjects in the combination therapy group and five subjects in the monotherapy group were excluded from the per protocol set (PPS) for various reasons such as receiving a low dose of bexarotene (Fig. 1). The FAS was used for the efficacy analysis in this study.

Efficacy

Table 1 shows the background information of the subjects included in the SAS at the commencement of treatment. Mean age (mean [SD])

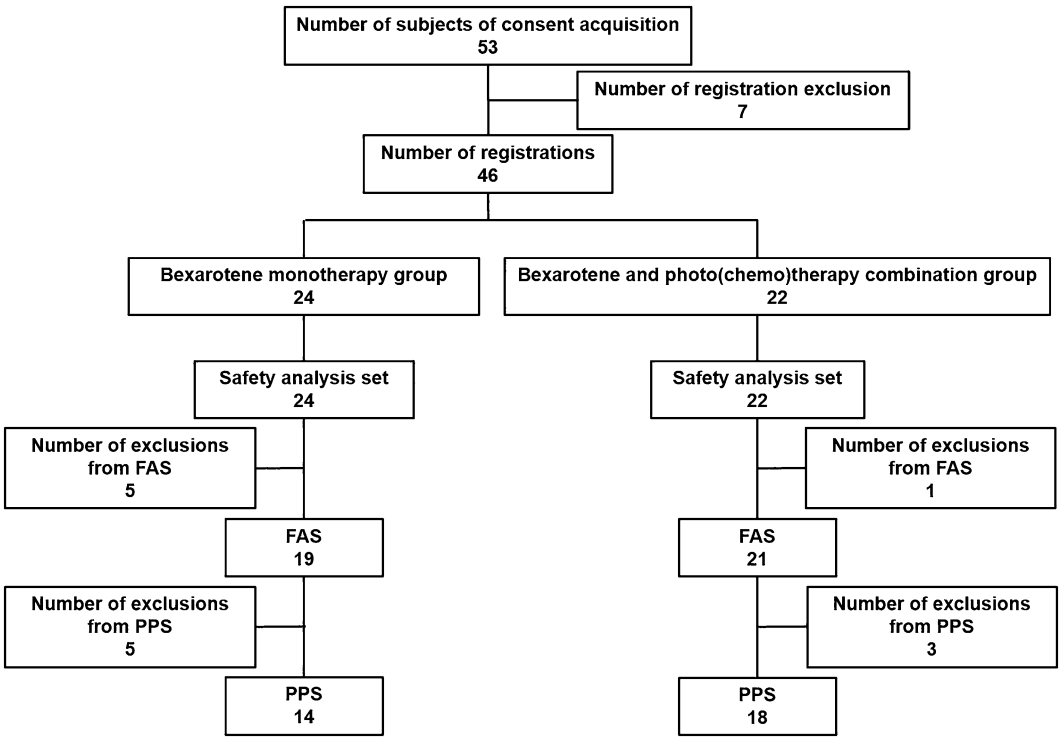

Fig. 1 Study design and subject flow chart. *FAS* full analysis set, *PPS* per protocol set

Table 1 Baseline characteristics of patients with CTCL

Category	Summary Statistics	Whole	Combination therapy	Monotherapy
Sex	Male/female	29 (63.0)/17 (37.0)	14 (63.6)/8 (36.4)	15 (62.5)/9 (37.5)
Age category (years)	Mean ± SD	69.3 ± 12.2	68.3 ± 13.3	70.3 ± 11.3
	Range	31–91	31–91	42–84
	< 50	4 (8.7)	2 (9.1)	2 (8.3)
	≥ 50 to < 60	5 (10.9)	3 (13.6)	2 (8.3)
	≥ 60 to < 70	8 (17.4)	3 (13.6)	5 (20.8)
	≥ 70 to < 80	20 (43.5)	11 (50.0)	9 (37.5)
	≥ 80	9 (19.6)	3 (13.6)	6 (25.0)
During of CTCL (years)	Mean ± SD	2.1 ± 5.7	1.9 ± 5.2	2.2 ± 6.3
	Range	0.0–28.7	0.0–21.4	0.0–28.7
Type of CTCL	Mycosis fungoides	40 (87.0)	19 (86.4)	21 (87.5)
	Sézary syndrome	0 (0.0)	0 (0.0)	0 (0.0)
	Others	6 (13.0)	3 (13.6)	3 (12.5)
Phase	≤ IIA	42 (91.3)	21 (95.5)	21 (87.5)
	≥ IIB	4 (8.7)	1 (4.5)	3 (12.5)
BSA (m^2)	Mean ± SD	1.6 ± 0.2	1.7 ± 0.2	1.6 ± 0.1
	Range	1.3–2.1	1.3–2.1	1.3–1.8

Data are expressed as number (%)
CTCL cutaneous T-cell lymphoma, *SD* standard deviation, *BSA* body surface area

in the combination therapy group was 68.3 [13.3] years (14 men [63.6%] and 8 women [36.4%]). Mean age (mean [SD]) in the monotherapy group was 70.3 [11.3] years (15 men [62.5%] and 9 women [37.5%]). Mean disease duration was 1.9 ± 5.2 years (combination therapy group) and 2.2 ± 6.3 years (monotherapy group). The CTCL disease type was MF in 19 subjects (86.4%) in the combination therapy group and 21 subjects (87.5%) in the monotherapy group; 3 subjects in each group had a different type of CTCL. The MF stage at the time of definite diagnosis was stage IIA or lower in 21 subjects (95.5%) in the combination therapy group and in 21 (87.5%) in the monotherapy group. One subject (4.5%) in the combination therapy group and three subjects (12.5%) in the monotherapy group had stage IIB or higher. Mean body surface area (mean [SD]) was 1.7 [0.2] m^2 in the combination therapy group and 1.6 [0.1] m^2 in the monotherapy group. The main comorbidities were cataracts, hypertension, and dyslipidemia in the combination therapy group and hypertension, cataract, and hyperuricemia in the monotherapy group.

In the combination therapy group, 21 subjects received bath-PUVA as the photo(chemo)therapy with an integrated irradiation dose of 75.3 [34.7] J/cm^2 and 7 received narrowband UVB at an integrated dose of 11.2 [8.3] J/cm^2.

The results of the general skin lesion evaluation using the mSWAT at 8 weeks after the initiation of the study and the response rate of PR or better (CCR + CR + PR) are summarized in Table 2 (Supplementary Fig. 1). Regarding the response rate of PR or better, no difference was

Table 2 Results of the mSWAT general skin lesion evaluation and the comprehensive evaluation of PGA

Group	mSWAT			PGA		
Whole	CCR	1 (2.6)	CCR + CR + PR	CCR	4 (10.3)	CCR + PR
	CR	3 (7.7)	32 (82.1)			33 (84.6)
	PR	28 (71.8)		PR	29 (74.4)	
	SD	7 (17.9)	SD + PD	SD	6 (15.4)	SD + PD
	PD	0 (0.0)	7 (17.9)	PD	0 (0.0)	6 (15.4)
Bexarotene and photo(chemo)therapy combination therapy group	CCR	1 (4.8)	CCR + CR + PR	CCR	4 (19.0)	CCR + PR
	CR	3 (14.3)	17 (81.0)			19 (90.5)
	PR	13 (61.9)		PR	15 (71.4)	
	SD	4 (19.0)	SD + PD	SD	2 (9.5)	SD + PD
	PD	0 (0.0)	4 (19.0)	PD	0 (0.0)	2 (9.5)
Bexarotene monotherapy group	CCR	0 (0.0)	CCR + CR + PR	CCR	0 (0.0)	CCR + PR
	CR	0 (0.0)	15 (83.3)			14 (77.8)
	PR	15 (83.3)		PR	14 (77.8)	
	SD	3 (16.7)	SD + PD	SD	4 (22.2)	SD + PD
	PD	0 (0.0)	3 (16.7)	PD	0 (0.0)	4 (22.2)

Data are expressed as number (%)

CCR clinical complete response, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

observed between the combination therapy group and the monotherapy group in 81.0% (95% CI [58.1, 94.6]) and 83.3% (95% CI [58.6, 96.4]), respectively. The response rates of CR or better (CCR + CR) in the combination therapy group and monotherapy group were 19.0% (4 subjects) and 0.0%, respectively. Although no significant difference was observed, the response rate was higher in the combination therapy group. The change in mSWAT score over time was not significantly different between groups, but at each evaluation period, both groups had a significantly lower score compared with that at the start of treatment ($p < 0.001$), indicating that the mSWAT score decreased over time (Fig. 2).

The best overall response up to 8 weeks using the mSWAT scores is illustrated in Fig. 3 using waterfall plots. The waterfall plots showed a higher rate of skin lesion resolution in patients with a PR in the combination group.

The results of the comprehensive evaluation by physicians using the PGA after 8 weeks of treatment were aggregated to the response rate of PR or better (CCR + PR) in Table 3 (Supplementary Fig. 2). At the time of evaluation after 8 weeks, the response rate of the overall evaluation using the PGA was 90.5% (95% CI [69.6, 98.8]) in the combination therapy group and 77.8% (95% CI [52.4, 93.6]) in the monotherapy group. The difference between groups was not statistically significant.

Based on the mSWAT score, the time to response (TTR) and time to PD (TTP) were calculated. The TTR from the date of commencing treatment to the time when the PR was confirmed for the first time was calculated using survival time analysis. The subjects that did not reach a PR by the time of the final evaluation were excluded from the final evaluation. The median TTR was 21.0 days (95% CI [18.0, 22.0]) for the combination therapy group and

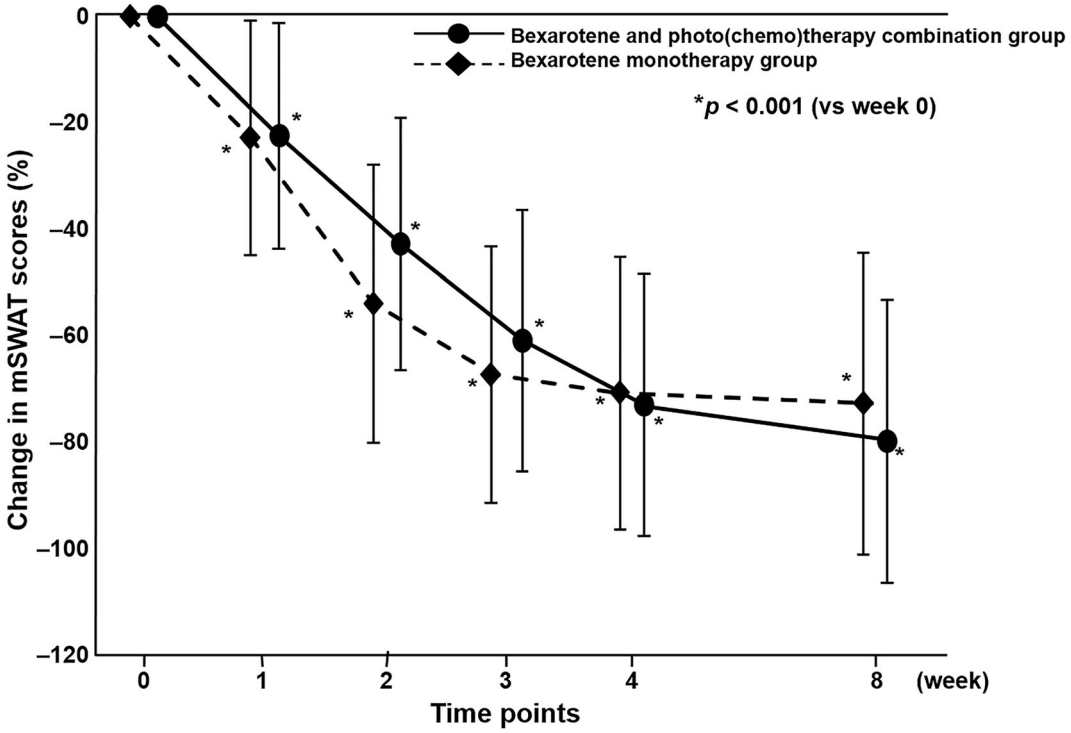

Fig. 2 Percentage change of overall cutaneous lesions based on the modified Severity-Weighted Assessment Tool (mSWAT) score. Circles with a solid line and rhombi with a dotted line indicate the bexarotene and photo(chemo)therapy combination group and the bexarotene monotherapy group, respectively. Error bars represented standard deviation. *$p < 0.001$ versus week 0

16.0 days (95% CI [14.0, 21.0]) for the monotherapy group. The difference between groups was not statistically significant (Fig. 4).

The TTP from the commencement of treatment to the time when it was determined to be advanced (PD) for the first time was calculated but could not calculate it because no cases showed disease progression.

Safety

All reported AEs were aggregated for the SAS. The major AEs reported are shown in Table 4. AEs were reported in all subjects, with a total of 231 events. The most severe AEs were hypertriglyceridemia, type 2 diabetes mellitus, acute cholecystitis, rhabdomyolysis, and interstitial lung disease.

A total of 164 adverse drug reactions (ADRs) occurred in all subjects (Table 4). The most serious ADRs reported were hypertriglyceridemia, rhabdomyolysis, and interstitial lung disease. The severity of other ADRs was mild to moderate. The ADRs with a high incidence were hypothyroidism, hypertriglyceridemia, hypercholesterolemia, and neutropenia. No new AEs or ADRs were reported that are not described in the package insert of the research drug.

DISCUSSION

The treatment strategy for malignant lymphoma is determined by the pathologic diagnosis, disease stage classification, and prognosis assessment [9]. The available therapeutic methods include skin-directed therapies, such as topical application, photo(chemo)therapy and radiation therapy, and systemic therapies, such as retinoid, interferon, and targeted therapies, alone or in combination. Skin-directed

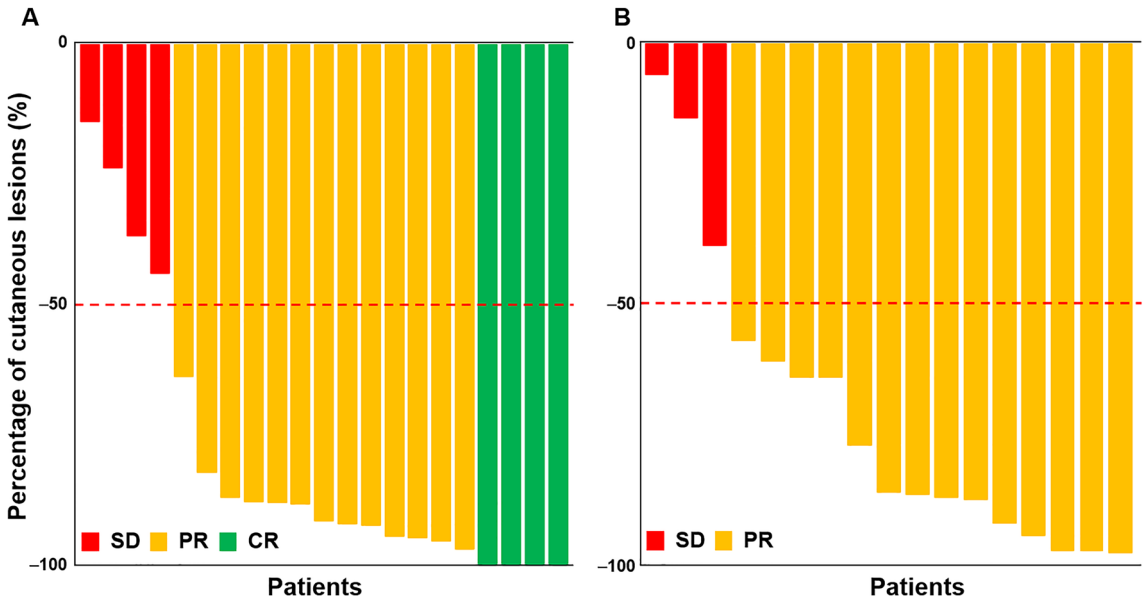

Fig. 3 Best overall responses in overall cutaneous lesions based on the mSWAT scores. **A** Bexarotene and photo(chemo)therapy combination group; **B** bexarotene monotherapy group. *CR* complete response, *PR* partial response, *SD* stable disease

therapies are applied as essential therapy, and systemic therapies are used for patients with advanced-stage disease.

Bexarotene is an anticancer agent classified as a retinoid that is used in the management of treatment-resistant CTCL with a high therapeutic effect even as a single agent. Duvic et al. reported that stage IA to IIA MF patients administered 300 mg/m^2 bexarotene alone showed a response rate of 54% and a CR rate of 7% [14].

Photo(chemo)therapy (e.g., PUVA, narrowband UVB, and excimer light) is a skin-directed therapy used in combination with topical steroids that is widely used to control disease progression in patients with early-stage MF (stage IA, IB, and IIA). In a retrospective study of UV radiation therapy for patients with early-stage MF, Ahmad et al. reported that narrowband UVB therapy yielded a CR in 50% (6/12) and a PR in 33% (4/12) of patients, while PUVA yielded a CR in 64% (18/28) and a PR in 21% (6/28) of patients [15]. In another study by Whittaker et al., UV irradiation treatment in early-stage MF produced good results with a stage progression rate in the IA and IB phases of 9–20% [16].

A phase III clinical trial (NCT00056056; 93 subjects) published in 2012 as the first study comparing bexarotene and PUVA combination therapy with PUVA monotherapy for early CTCL found no significant difference in the response rates between the two groups [17]. Subjects in the bexarotene and PUVA combination therapy group who demonstrated a response, however, appeared to require less UV irradiation compared with subjects in the PUVA monotherapy group. The combination therapy was considered to reduce resistance to photo(chemo)therapy and suppress photo(chemo)therapy-induced ADRs by decreasing the required dose of UV irradiation.

In the present study, the efficacy and safety were compared between bexarotene and photo(chemo)therapy combination therapy and bexarotene monotherapy in Japanese patients with CTCL. Regarding the primary endpoints of this study, the response rates by mSWAT and PGA evaluation after 8 weeks were high in both groups (over 80% by mSWAT evaluation), and no significant difference was observed between the two groups. In both groups, the mSWAT scores decreased over the

Table 3 Adverse events

	Whole		Combination therapy		Monotherapy	
	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Adverse events (overall)	46 (100.0)	231	22 (100.0)	111	24 (100.0)	120
Metabolic and nutritional disorders	44 (95.7)	83	21 (95.5)	39	23 (95.8)	44
Hypertriglyceridemia	42 (91.3)	42	21 (95.5)	21	21 (87.5)	21
Hypercholesterolemia	31 (67.4)	31	14 (63.6)	14	17 (70.8)	17
Hyperuricemia	3 (6.5)	3	1 (4.5)	1	2 (8.3)	2
Hypoalbuminemia	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Type 2 diabetes	1 (2.2)	1	0 (0.0)	0	1 (4.2)	1
Endocrine disorders	43 (93.5)	43	22 (100.0)	22	21 (87.5)	21
Hypothyroidism	43 (93.5)	43	22 (100.0)	22	21 (87.5)	21
Laboratory test	24 (52.2)	27	10 (45.5)	10	14 (58.3)	17
CRP increase	17 (37.0)	17	7 (31.8)	7	10 (41.7)	10
Increased platelet count	6 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Increased blood creatine phosphokinase	6 (6.5)	3	0 (0.0)	0	3 (12.5)	3
Blood and lymphatic disorders	19 (41.3)	23	9 (40.9)	11	10 (41.7)	12
Neutropenia	16 (34.8)	16	7 (31.8)	7	9 (37.5)	9
Anemia	5 (10.9)	5	3 (13.6)	3	2 (8.3)	2
Gastrointestinal disorders	8 (17.4)	10	3 (13.6)	5	5 (20.8)	5
Coprostasis	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Hepatic biliary disorders	7 (15.2)	7	2 (9.1)	2	5 (20.8)	5
Liver function abnormality	6 (13.0)	6	2 (9.1)	2	4 (16.7)	4
Acute cholecystitis	1 (2.2)	1	0 (0.0)	0	1 (4.2)	1
General and systemic disorders and conditions at the site of administration	6 (13.0)	8	4 (18.2)	6	2 (8.3)	2
Fatigue	3 (6.5)	4	2 (9.1)	3	1 (4.2)	1
Skin and subcutaneous tissue disorders	4 (8.7)	6	3 (13.6)	5	1 (4.2)	1
Skin dryness	2 (4.3)	2	2 (9.1)	2	0 (0.0)	0
Musculoskeletal and connective tissue disorders	4 (8.7)	4	4 (4.5)	1	3 (12.5)	3
Rhabdomyolysis	1 (2.2)	1	0 (0.0)	0	1 (4.2)	1
Nervous system disorders	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Headache	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Respiratory, thorax, and longitudinal disorders	1 (2.2)	1	1 (4.5)	1	0 (0.0)	0

Table 3 continued

	Whole		Combination therapy		Monotherapy	
	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Interstitial lung disease	1 (2.2)	1	1 (4.5)	1	0 (0.0)	0

Data are expressed as number (%)

8-week study period, but four subjects in the bexarotene and photo(chemo)therapy combination therapy group had a CR or better (CCR + CR), leading to a lower final mean score in the combination therapy group. In our previous study, bexarotene and photo(chemo)therapy combination therapy led to a response rate (based on the mSWAT score) of 80% (20/25 patients) in the FAS and 75% (9/12 cases) in the PPS; even when limiting the disease stage to IIA or higher, the response rate was 75% (9/12 patients) in the PPS [11]. The subjects in this study had a high proportion of early-stage MF and high response rates by mSWAT and PGA evaluation after 8 weeks, suggesting that early diagnosis and early treatment are necessary for CTCL treatment. A case series study performed by Fujimura et al. indicated that a low initial dose of bexarotene (150–300 mg/body) combined with narrow-band UVB could be an optimal treatment for advanced-stage CTCL [18]. These findings

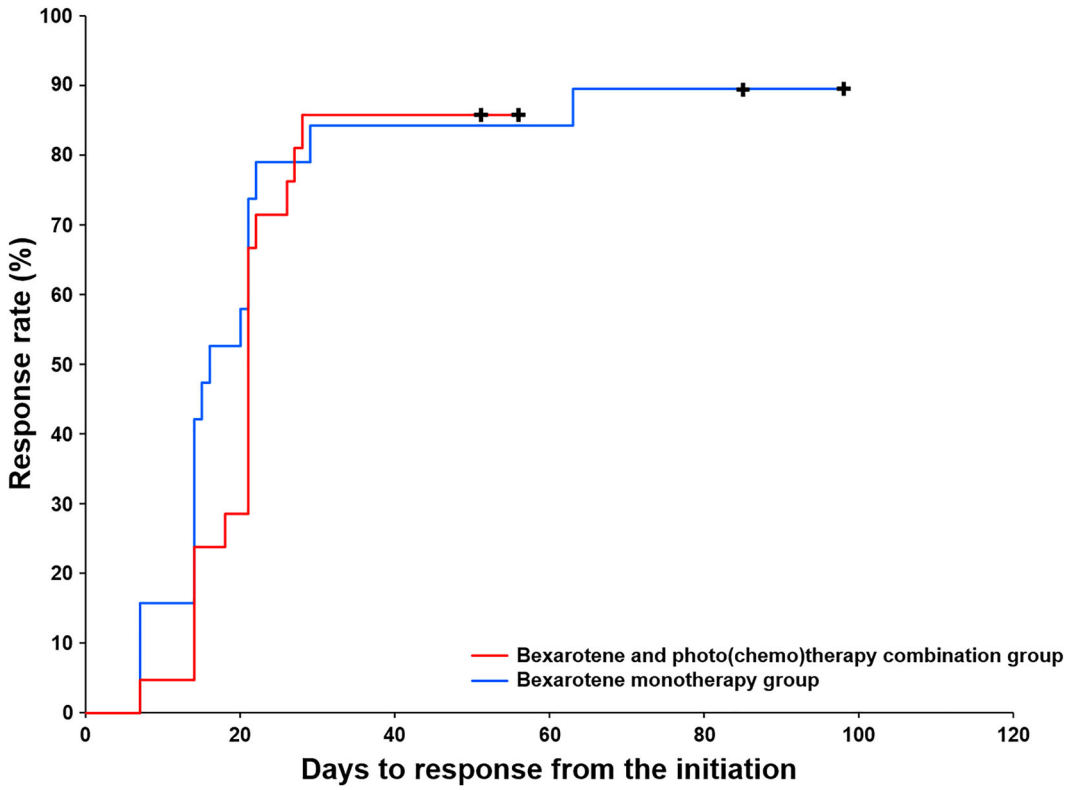

Fig. 4 Time to response (TTR) of the full analysis set. Red and blue lines indicate the bexarotene and photo(chemo)therapy combination group and the bexarotene monotherapy group, respectively

Table 4 Adverse events

	Whole		Combination therapy		Monotherapy	
	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Adverse events (overall)	46 (100.0)	231	22 (100.0)	111	24 (100.0)	120
Metabolic and nutritional disorders	44 (95.7)	83	21 (95.5)	39	23 (95.8)	44
Hypertriglyceridemia	42 (91.3)	42	21 (95.5)	21	21 (87.5)	21
Hypercholesterolemia	31 (67.4)	31	14 (63.6)	14	17 (70.8)	17
Hyperuricemia	3 (6.5)	3	1 (4.5)	1	2 (8.3)	2
Hypoalbuminemia	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Type 2 diabetes	1 (2.2)	1	0 (0.0)	0	1 (4.2)	1
Endocrine disorders	43 (93.5)	43	22 (100.0)	22	21 (87.5)	21
Hypothyroidism	43 (93.5)	43	22 (100.0)	22	21 (87.5)	21
Laboratory test	24 (52.2)	27	10 (45.5)	10	14 (58.3)	17
CRP increase	17 (37.0)	17	7 (31.8)	7	10 (41.7)	10
Increased platelet count	6 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Increased blood creatine phosphokinase	6 (6.5)	3	0 (0.0)	0	3 (12.5)	3
Blood and lymphatic disorders	19 (41.3)	23	9 (40.9)	11	10 (41.7)	12
Neutropenia	16 (34.8)	16	7 (31.8)	7	9 (37.5)	9
Anemia	5 (10.9)	5	3 (13.6)	3	2 (8.3)	2
Gastrointestinal disorders	8 (17.4)	10	3 (13.6)	5	5 (20.8)	5
Coprostasis	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Hepatic biliary disorders	7 (15.2)	7	2 (9.1)	2	5 (20.8)	5
Liver function abnormality	6 (13.0)	6	2 (9.1)	2	4 (16.7)	4
Acute cholecystitis	1 (2.2)	1	0 (0.0)	0	1 (4.2)	1
General and systemic disorders and conditions at the site of administration	6 (13.0)	8	4 (18.2)	6	2 (8.3)	2
Fatigue	3 (6.5)	4	2 (9.1)	3	1 (4.2)	1
Skin and subcutaneous tissue disorders	4 (8.7)	6	3 (13.6)	5	1 (4.2)	1
Skin dryness	2 (4.3)	2	2 (9.1)	2	0 (0.0)	0

Table 4 continued

	Whole		Combination therapy		Monotherapy	
	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Musculoskeletal and connective tissue disorders	4 (8.7)	4	4 (4.5)	1	3 (12.5)	3
Rhabdomyolysis	1 (2.2)	1	0 (0.0)	0	1 (4.2)	1
Nervous system disorders	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Headache	3 (6.5)	3	2 (9.1)	2	1 (4.2)	1
Respiratory, thorax, and longitudinal disorders	1 (2.2)	1	1 (4.5)	1	0 (0.0)	0
Interstitial lung disease	1 (2.2)	1	1 (4.5)	1	0 (0.0)	0

Data are expressed as number (%)

suggest the usefulness of bexarotene as adjuvant therapy for photo(chemo)therapy.

The results of the mSWAT and PGA evaluations after 8 weeks did not differ significantly between the two groups. Our study results are consistent with the findings of Whittaker et al. [17], who reported no significant difference in the response rate or response duration in a randomized clinical trial of bexarotene and PUVA combination therapy and bexarotene monotherapy in European early-stage MF patients; the best overall response rate was 71% for PUVA monotherapy and 77% for combination therapy. In the present study, the integrated irradiation dose in PUVA was 75.3 ± 34.7 J/cm^2, comparable to that in Whittaker et al. (101.7 J/cm^2) [17].

The two groups did not differ in terms of the TTR and the TTP by mSWAT evaluation, which are secondary endpoints, because response rates in both groups reached > 80% within 30 days. The high response rate in the present study is likely attributable to: (1) the inclusion of many early-stage MF patients and (2) topical application of various steroids. These findings suggest the usefulness of bexarotene for earlier resolution of skin symptoms in early-stage MF patients.

Although ADRs of bexarotene are reported in Japan and elsewhere, none were specific to this study. There were three cases of discontinuation of the study due to ADRs. The AEs and ADRs that occurred were reported, with a total of 231 and 164 events, respectively. The AEs and ADRs that occurred frequently were hypothyroidism, hypertriglyceridemia, hypercholesterolemia, and neutropenia, all of which are known. Serious AEs and ADRs were observed in five events in five subjects, and in three events in three subjects, respectively, but all patients recovered after receiving medical treatment.

Bexarotene exhibits phototoxicity in in vitro tests (photo-hemolytic test and histidine photo-oxidation reaction) [19]. In previous studies, non-serious photosensitivity was reported among those receiving combination therapy with UVB irradiation: 6.3% (1/16) patients in a phase I/II study (B-1101 study) in Japan [19, 20], 1.7% (1/59) patients in a phase IV study (E7273-G000-401 study) (2019, pers. comm.), and 1.7% (1/58) patients in phase II/III study (L1069-23 study) performed in the US [21]. No photosensitivity was reported in the present study.

CONCLUSIONS

This study revealed no statistical difference in the therapeutic effect between combined bexarotene and photo(chemo)therapy and bexarotene monotherapy based on the mSWAT and PGA evaluation after 8 weeks. Both the combination therapy and monotherapy, however,

were efficacious for the management of CTCL. Moreover, in the bexarotene and photo(chemo)therapy combination group, some patients showed a complete response, suggesting that the combination of both bexarotene and photo(chemo)therapy has a greater therapeutic effect than bexarotene monotherapy in Japanese patients with CTCL.

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Compliance with Ethical Guidelines. This study was conducted in accordance with protocols reviewed and approved by Nagoya City University Hospital Clinical Research Review board and conformed to the ethical principles of the Declaration of Helsinki (revised 2013) and the Clinical Trials Act in Japan. In the case of multicenter specified clinical study under the Clinical Trials Act, after approval by the central Certified Review Board (CRB), the implementation permission of the administrator of each implementing medical institution has been obtained. The outline of this study is registered and published in the Japan Registry of Clinical Trials (jRCT) (Trial ID; jRCTs041180094). The patients provided written informed consent for publication of any identifying information after receiving an explanation of the study.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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