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Results from a Phase I/II Open-Label, Dose-Finding Study of Pralatrexate and Oral Bexarotene in Patients with Relapsed/Refractory Cutaneous T-cell Lymphoma

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Abstract

Purpose: Pralatrexate is a folic acid analogue metabolic inhibitor similar to methotrexate, which has shown tolerability and efficacy with an overall response rate of 45% in a phase I dose deescalation study of patients with relapsed/refractory cutaneous T-cell lymphoma (CTCL).

Experimental Design: The object of this phase I/II open-label, multicenter clinical trial was to determine the MTD and recommended dose of pralatrexate plus oral bexarotene in 34 patients with relapsed/refractory CTCL who had failed prior systemic therapies. Pralatrexate was administered by intravenous push at 15 mg/m^2 given weekly 3 weeks out of 4 weeks with daily oral bexarotene (150 or 300 mg/m^2), levothyroxine, atorvastatin, folate, and with B12 every 2 months.

Results: At the MTD of 15 mg/m^2 bexarotene and 15 mg/m^2 pralatrexate, the response rate was 60% [4 complete responses (CR), 14 partial responses (PR)], the maximum observed response duration was 28.9+ months, and duration of response for 4 CRs ranged from 9.0 to 28.3 months. The median progression-free survival was 12.8 months (0.5–29.9). Mucositis was the most common adverse event.

Conclusions: The combination of pralatrexate (15 mg/m^2) and oral bexarotene (150 mg/m^2) is active with high response rates and minimal toxicity for cutaneous T-cell lymphomas. *Clin Cancer Res; 23(14); 3552–6. ©2017 AACR.*

Introduction

Cutaneous T-cell lymphomas (CTCL) are extranodal, non-Hodgkin lymphomas, distinguished by their clinical features and clonal T-cell surface receptors (1). The most common subtype of CTCL is mycosis fungoides accounting for 60% of new diagnoses, with Sézary syndrome or erythrodermic, leukemic variant representing 10%, and CD30$^+$ primary cutaneous anaplastic T-cell lymphoma (ALCL) 20%. Although mycosis fungoides patients often have an indolent course limited to skin patches and/or plaques, mycosis fungoides patients with tumors, extracutaneous disease, and large cell transformation experience a more aggressive disease behavior and have a worse overall survival (2–4). Skin-directed therapies are preferred for early-stage mycosis fungoides (T1, T2), but patients with transformed mycosis fungoides and advanced stages need additional systemic therapy. Currently available systemic therapies have demonstrated response rates of 25% to 50% (5–8).

Pralatrexate is an antifolate (9, 10) with demonstrated tolerability and activity in subjects with relapsed/refractory peripheral T-cell lymphoma (PTCL) and CTCL. However, the approved dose of pralatrexate for PTCL is 30 mg/m^2 weekly for 6 of 7 weeks (10, 11). In a CTCL-specific study, the dose of 15 mg/m^2 pralatrexate given weekly 3 of 4 weeks was identified as active and was better tolerated than the full standard dosing with an overall response rate of 45% among patients with relapsed or refractory disease (12). The dose-limiting toxicity (DLT) for pralatrexate is mucositis (12); bexarotene induces central hypothyroidism and hypertriglyceridemia (13). The overall response rate in advanced mycosis fungoides patients treated with an initial dose of 300 mg/m^2/day of oral bexarotene was 45% (13). Heterogeneous patient populations and evolving staging criteria over time do not allow head to head comparisons of response rates. Preclinical studies in mycosis fungoides/Sézary syndrome cell lines, patients' Sézary cells, and a mouse xenograft model support the hypothesis that pralatrexate combined with bexarotene may be synergistic in human subjects (Xiang, unpublished data).

The object of this phase I/II open-label, multicenter clinical trial was to determine the MTD and recommended dose of pralatrexate plus oral bexarotene in patients with relapsed/refractory CTCL who had failed prior systemic therapies.

Materials and Methods

Study design

This was a multicenter, open-label, nonrandomized dose-finding study (PDX-018; NCT01134341) conducted between July 15, 2010, and March 9, 2015. It followed a standard 3 + 3 dose escalation design to determine the MTD using the dose levels in Table 1. The study was conducted in accordance with the Good Clinical Practices in accordance with the U.S. Department of Health and Human Services. All patients signed informed consent approved by each center's IRB. As shown in Fig. 1, pralatrexate was

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Translational Relevance

The two major variants of cutaneous T-cell lymphoma, mycosis fungoides, and Sézary syndrome are currently incurable, and approved agents have response rates of around 30% to 35%. In this phase I/II dose escalation trial, we tested the combination of two active agents, bexarotene, the first rexinoid, and pralatrexate, a powerful folic acid inhibitor. Preliminary *in vitro* and *ex vivo* studies conducted in T-cell lymphoma cell lines, Sézary cells, and immunodeficient mice supported the synergism of the two agents and formed the basis for this phase II clinical trial. The combination of pralatrexate (15 mg/m_2 3 weeks out of 4) and bexarotene (150 mg daily) gave a superior response rate of 60% compared with 45% and 35%, respectively, and long-term responses were seen.

administered by intravenous infusion of 30 seconds to 5 minutes once weekly for 3 weeks of a 4-week treatment cycle. Subjects could be treated until progression or intolerance. Bexarotene was self-administered orally once daily with food. Vitamin B12 (1 mg i.m. every 8–10 weeks) and folic acid (1–1.25 mg orally once daily) were supplements administered at least 7 days prior to initiation of the study treatment and continued until 30 days after the last dose of study drug.

Inclusion/exclusion criteria

CTCL patients with mycosis fungoides stage ≥IB, Sézary syndrome, or primary cutaneous anaplastic large cell lymphoma were eligible if they had relapsed or were refractory to at least one prior systemic therapy or were intolerant to their last prior therapy. The required ECOG status was 0 to 2. Exclusion criteria included having a history of prior malignancies with disease-free duration <5 years unless treatment resulted in complete resolution with no current clinical, radiologic, or laboratory evidence of active or recurrent disease. Patients with active central nervous system disease, uncontrolled hypercholesterolemia or hypertriglyceridemia, and previous exposure to pralatrexate were excluded. Oral retinoids, except bexarotene, within 4 weeks of study treatment or high-dose vitamin A were not allowed.

Response criteria

Global response criteria were used to assess response to the therapy (Table 2). The modified skin weighted assessment tool (mSWAT) was used to assess the extent of skin disease, flow cytometry was used to measure blood involvement, and CT scans were used for assessing nodal involvement (14). Complete response (CR) was defined as 100% clearance of disease in all areas (skin, blood, viscera, and lymph nodes), and partial response was 50% improvement in all of the above. Stable disease was <25% increase to <50% reduction in mSWAT from baseline or failure to meet criteria for CR, partial response (PR), or progressive disease (PD). PD was defined as a ≥25% increase in mSWAT score from baseline or, in patients who achieved CR or PR, as a ≥25% increase of mSWAT score from the sum of nadir and 50% baseline mSWAT scores.

Table 1. Patient cohorts and drug escalation criteria

Cohorts	Pralatrexate dose (i.v.)	Bexarotene dose[a] (p.o.)
Cohort 1	15 mg/m^2	150 mg/m^2
Cohort 2a	15 mg/m^2	300 mg/m^2
Cohort 2b	10 mg/m^2	150 mg/m^2
Cohort 3	10 mg/m^2	300 mg/m^2

Abbreviation: p.o., orally.
[a]Dose of bexarotene determined by guidelines per package insert.

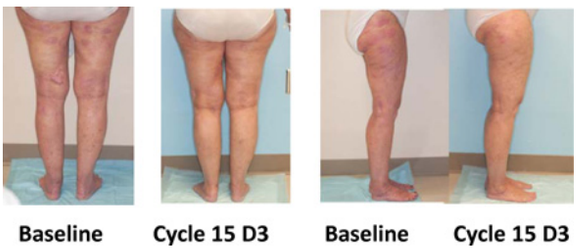

Figure 1.
Clinical PR to pralatrexate and bexarotene comparing baseline with course 15 day 3. The patient was on the drug for over 2 years with almost complete CR.

Results

Demographics and DLT

The disposition of patients in each cohort is shown in Table 3. For all patients, the median prior therapies was 3.5 (1–14). Eighteen patients (53%) had prior bexarotene exposure, including 2 of 4 with CRs and 10 of 16 with PRs. The demographics and CTCL subtypes at baseline are shown in Table 4. The patient exposure to each drug is in Table 5. Patients who had a baseline evaluation and received all three doses of pralatrexate in the first cycle or had a DLT were evaluable for efficacy. No DLTs were observed at dose level 1 (pralatrexate 15 mg/m^2 and bexarotene 150 mg/m^2). Of 3 patients in the second cohort who received pralatrexate 15 mg/m^2 with bexarotene 300 mg/m^2 at dose level 2, two had DLTs during cycle 1. One patient had grade 2 hypotension and grade 3 neutropenia and the other had grade 4 thrombocytopenia and neutropenia. An additional 3 subjects were enrolled on dose level 1, and 0 of 3 experienced a DLT. Level 1 was then determined to be the MTD. Overall, 33 of 34 evaluable patients with relapsed or refractory CTCL were treated with up to 33 cycles of combination therapy.

Table 2. Global response: criteria for integrated response evaluation

Response designation	Criteria
CR	• 100% clearance of disease in all areas (skin, blood, viscera, lymph nodes)
PR	• 50% disease reduction in all involved areas
Stable disease	• <25% increase to <50% reduction in mSWAT score from baseline • Failure to meet criteria for CR, PR, or PD
PD	• ≥25% increase in mSWAT score from baseline • In patients with CR or PR, ≥25% increase of mSWAT score from the sum of nadir and 50% baseline mSWAT score

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Table 3. Patient disposition: safety population[a]

Parameter	Cohort 1/ expansion ($n = 31$)	Cohort 2a ($n = 3$)	All patients ($N = 34$)
Discontinuation of treatment, *n* (%)	31 (100)	3 (100)	34 (100)
Primary reasons for treatment discontinuation, *n* (%)			
AE	11 (35)	0 (0)	11 (32)
Disease progression	7 (23)	2 (67)	9 (26)
Patient decision	6 (19)	1 (33)	7 (21)
Investigator decision	4 (13)	0 (0)	4 (12)
Initiation of subsequent therapy	2 (6)	0 (0)	2 (6)
Sponsor decision	1 (3)	0 (0)	1 (3)

[a]Included all patients who received at least 1 dose of pralatrexate or bexarotene.

Efficacy

The response rate (CR + PR) in 33 evaluable patients who had a baseline exam and received at least one dose of medication was 61%. One patient was not evaluable because they only received two doses of pralatrexate. Response by each CTCL subtype is shown in Table 7. Of note, the response rate was 65% in Sézary syndrome and 50% in transformed mycosis fungoides. CRs were seen in one ALCL, one IIB, and two IVA2 mycosis fungoides patients. PRs were seen in one transformed IA, three IV, three IIA, seven IIB, and one each III, IVA1, and IVB. Stable disease was seen in one IV, I t-IIB, one III, one IVA1, four IVA2, and two unknown. Two IB patients had stable disease. Figure 1 shows an example of a patient with transformed mycosis fungoides who achieved a long-lasting PR for over 2 years. Study treatment also provided a potential survival benefit to patients, with a median PFS of 12.8 months (range 0.5–29.9+ months) at the MTD. The probability of remaining in response, estimated using the Kaplan–Meier method, was 89.1% at 3 months, 79.1% at 6 months, 72.5% at 9 months, and 57.7% at 12 months.

Safety

The most common reasons for discontinuation on the protocol were adverse events (AE; 32%), PD (26%), or decision of investigator or patient (32%; Table 3).

Table 4. Baseline characteristics

Characteristics	Cohort 1/ expansion ($n = 31$)	Cohort 2a ($n = 3$)	All patients ($N = 34$)
Median age, y (range)	66 (41–85)	55 (39–77)	66 (39–85)
Age ≥65 y, *n* (%)	18 (58)	1 (33)	19 (56)
Male, *n* (%)	16 (52)	2 (67)	18 (53)
Median BSA, m^2 (range)	1.82 (1.49–2.45)	2.00 (1.95–2.35)	1.86 (1.49–2.45)
Histology at study entry, *n* (%)			
MF	17 (55)	2 (67)	19 (56)
Transformed MF	10 (32)	1 (33)	11 (32)
Sézary syndrome	3 (10)	0 (0)	3 (9)
Primary cutaneous ALCL, ALK^-	1 (3)	0 (0)	1 (3)
ECOG performance status 0/1/2, %	68/16/16	67/33/0	68/18/15
Median number of prior therapies (range)	3 (1–12)	4 (3–14)	3.5 (1–14)

Abbreviations: BSA, body surface area; MF, mycosis fungoides.

Table 5. Exposure to study treatments: safety population[a]

Parameter	Cohort 1/ expansion ($n = 31$)	Cohort 2a ($n = 3$)	All patients ($N = 34$)
Exposure to pralatrexate			
Median number of cycles (range)	6 (1–33)	5 (2–9)	5.5 (1–33)
Median number of doses (range)	15 (2–84)	10 (2–24)	14 (2–84)
Median total dose, mg/m^2 (range)	227.8 (30–1,238)	113.4 (30–360)	205.5 (30–1,238)
Dose reductions, *n* (%)	8 (26)	1 (33)	9 (26)
Exposure to bexarotene			
Median number of cycles (range)	6 (1–33)	5 (2–9)	6 (1–33)
Median duration, days (range)	168.5 (15–916)	127 (30–240)	168 (15–916)
Dose reductions, *n* (%)	9 (29)	1 (33)	10 (29)

[a]Included all patients who received at least 1 dose of pralatrexate or bexarotene.

In the last group who did complete one cycle, six discontinued for lack of efficacy, one had worsening Parkinson disease, one had difficult venous access, and one was concerned about recurrent venous access. AEs reported in ≥20% patients are shown in Table 6. The most common events at any grade were stomatitis/mucositis, fatigue, hypertriglyceridemia, nausea, and neutropenia. The most common AEs of any grade considered attributed to pralatrexate by the investigator included stomatitis (65%), fatigue (44%), nausea (32%), neutropenia (32%), and anemia (24%). The most common AEs considered attributed to bexarotene by the investigator included hypertriglyceridemia (56%), fatigue (44%), neutropenia (32%), nausea (26%), and central hypothyroidism (24%). As both drugs can cause anemia, fatigue, and neutropenia, it was not possible to determine whether bexarotene or pralatrexate or both were responsible.

Grade 3 and 4 AEs are shown in Table 6 and included stomatitis, hypertriglyceridemia, and neutropenia. Grade 3/4 hematology values were reported for a total of 19 patients (56%) on study, including 17 patients (50%) with grade 3 values and 4 patients (12%) with grade 4 values. Hematology parameters that were observed at a severity of grade 3/4 included lymphocyte and neutrophil counts (each 32%), WBC counts (12%), platelet counts (9%), and hemoglobin (3%). Grade 3 serum chemistry values were reported for 14 patients (41%), most of which (13/14 patients) involved elevated triglycerides.

Table 6. Treatment-emergent AEs experienced by ≥20% of patients ($N = 34$)

AE	Any grade, *n* (%)	Grade 3 or 4, *n* (%)
Stomatitis	23 (68)	7 (21)
Fatigue	19 (56)	0
Hypertriglyceridemia	19 (56)	10 (29)
Nausea	16 (47)	0
Neutropenia	12 (35)	12 (35)
Peripheral edema	11 (32)	2 (6)
Anemia	10 (29)	1 (3)
Skin infection	9 (26)	2 (6)
Cough	8 (24)	0
Diarrhea	8 (24)	2 (6)
Dizziness	8 (24)	1 (3)
Dyspnea	8 (24)	2 (6)
Hypothyroidism	8 (24)	0
Pain in extremity	7 (21)	0

Table 7. Response by CTCL subtype

CTCL subtype	ORR	CR	PR
All evaluable patients ($N = 33$)[a]	20 (61%)	4 (12%)	16 (48%)
MF ($n = 19$)	12 (63%)	2 (11%)	10 (53%)
Transformed MF ($n = 10$)	5 (50%)	1 (10%)	4 (40%)
Sézary syndrome ($n = 3$)	2 (67%)	0 (0)	2 (67%)
ALCL ($n = 1$)	1 (100%)	1 (100%)	0 (0)
Stage of MF responders		IIB, IVA2(2)	t-IA;IB(3);IIa (3); IIb(7); & III;IVA1;IVB (1)

Abbreviations: MF, mycosis fungoides; t, transformed.
[a]Included all patients who received at least 1 dose of pralatrexate or bexarotene and had a baseline response evaluation.

Dose reductions were made in 21% of the patients. Dose omissions due to AEs occurred in 6% of patients. Dose reductions due to bexarotene-related AEs occurred in 24% of patients. Dose omissions due to bexarotene AEs occurred in 59% of patients. Fifteen percent of patients experienced both pralatrexate and bexarotene reductions, and 50% of patients experienced both pralatrexate and bexarotene omission.

Conclusions

The combination of pralatrexate and bexarotene was well tolerated with a safety profile consistent with that observed previously with the individual study drugs. No patient deaths were attributed to either study treatment. The MTD identified in this study (pralatrexate 15 mg/m^2 given weekly 3 out of 4 weeks and bexarotene 150 mg/m^2 daily) is the recommended dose for future clinical trials using this combination. The combination of low pralatrexate and bexarotene doses was associated with a higher overall response rate (61%) than response rate of 45% reported for pralatrexate or bexarotene alone (12, 13). The combination showed activity even among heavily pretreated patients and across the various CTCL subtypes, including 2 of 3 subjects with Sézary syndrome (67%) and 5 of 10 with transformed mycosis fungoides (50%; ref. 12). The overall response was 61% with 4 CRs and 14 PRs treated at the MTD. Remarkably, 67% of the patients treated at the MTD responded and maintained their response for >6 months. The median progression-free survival at the MTD was 12.8 months (range, 0.5–29.9). Thus, pralatrexate with bexarotene is capable of producing durable responses, even in patients with advanced disease such as blood involvement and with large-cell transformation and further investigation is warranted.

Disclosure of Potential Conflicts of Interest

M. Duvic reports receiving commercial research grants from Allos/Spectrum. S.M. Horwitz is a consultant/advisory board member for Celgene, Kyowa Hakka Kirin, Seattle Genetics, Spectrum, and Takeda. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: M. Duvic, S.M. Horwitz
Development of methodology: M. Duvic, P.L. Zinzani, S.M. Horwitz
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Duvic, Y.H. Kim, P.L. Zinzani, S.M. Horwitz
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Duvic, Y.H. Kim, P.L. Zinzani, S.M. Horwitz
Writing, review, and/or revision of the manuscript: M. Duvic, Y.H. Kim, P.L. Zinzani, S.M. Horwitz
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Duvic

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