Phase 1 and 2 Trial of Bexarotene Gel for Skin-Directed Treatment of Patients With Cutaneous T-Cell Lymphoma

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Objective: To evaluate the safety, dose tolerance, and efficacy of topical bexarotene gel in patients with early-stage cutaneous T-cell lymphoma (CTCL).

Design: Phase 1 and 2, open-label, dose-escalation clinical trial of bexarotene gel.

Setting: Three university-based clinics.

Participants: Sixty-seven adults with early-stage (TNM stages IA-IIA) CTCL.

Interventions: Bexarotene gel, 0.1%, 0.5%, and 1.0%, applied in incremental dose adjustments from 0.1% gel every day to 1.0% gel 4 times daily or the maximal tolerated dose.

Main Outcome Measures: Patients were followed for efficacy and safety, and treatment continued as long as they benefited. Response (≥50% improvement) was evaluated by the Physician’s Global Assessment of cutaneous disease and by an overall severity assessment of cutaneous disease, including signs of CTCL and area involved.

Results: Most patients tolerated topical bexarotene at 1% gel twice daily for routine use. Adverse events were generally mild to moderate in severity and were confined to treatment sites. Treatment-limiting toxic effects were associated with skin irritation and increased with gel exposure. Patients achieved an overall response rate of 63% and a clinical complete response rate of 21%. Median projected time to onset of response was 20.1 weeks (range, 4.0-86.0 weeks), and the estimated median response duration from the start of therapy was 99 weeks. Patients with no previous therapy for mycosis fungoides responded at a higher rate (75%) than those who previously underwent topical therapies (67%).

Conclusions: Bexarotene gel was well tolerated, was easily self-applied, and had a substantial response rate in treating patients with early-stage CTCL.

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Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of low-grade non-Hodgkin lymphomas that manifest primarily in the skin. Mean age at onset of disease is 50 to 56 years, and it is more common in men than in women (2.2:1.0) and in blacks than in whites (2:1). Approximately 1000 or more new cases of CTCL are diagnosed each year in the United States. The cause is unknown. Cutaneous T-cell lymphoma is characterized by the accumulation of a clonal population of helper (CD4+) T cells with hyperchromatic, irregularly shaped (cerebriform) nuclei in the epidermis and papillary dermis. The most common type of CTCL is mycosis fungoides (MF), which can progress through patch, plaque, and tumor phases and sometimes presents as erythroderma. The initial clinical presentation in early-stage MF is flat, erythematosus, hyperpigmented or hypopigmented patches typically found on sun-protected areas of the body. These skin patches may wax and wane for several years before being diagnosed. Confounding the diagnosis is the fact that MF lesions often respond to corticosteroids or treatments directed at psoriasis and other dermatoses. After the exclusion of other skin disorders, such as eczema, tinea, and psoriasis, a diagnosis of early-stage MF is derived from clinical and histological findings, but it is often difficult.

The clinical course of MF and other types of CTCL is variable. The stage at presentation is important in determining the patient’s prognosis and the therapeutic choices.

For editorial comment see page 398

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PATIENTS AND METHODS

A phase 1 and 2 multicenter trial of topical bexarotene gel was conducted in 67 patients with early-stage (TNM stages IA, IB, and IIA) CTCL from January 11, 1995, to March 23, 1998. The trial was conducted at 3 US study centers (Department of Dermatology, University of Cincinnati; Department of Dermatology, The University of Texas and M.D. Anderson Cancer Center; and Department of Oncology, Northwestern University) that had protocols of identical design approved by local institutional review boards.

STUDY DESIGN

The trial design was an open-label, dose-escalation, safety and efficacy evaluation of topically applied 0.1%, 0.5%, and 1.0% bexarotene gel concentrations. Patients began receiving 0.1% bexarotene gel once daily (QD) initially and escalated in dose every 2 weeks if tolerated to 0.1% twice daily (BID), 0.3% QD, 0.5% BID, 1.0% QD, and 1.0% BID, with the option to increase applications to up to 4 times a day (QID). After the safety and tolerability of 1.0% gel was established in the first 49 study patients, a protocol amendment required the remaining 18 patients to begin treatment at 1.0% gel every other day and to escalate gel applications stepwise (QD, BID, 3 times daily, and QID) at 1- to 2-week intervals, as tolerated.

PATIENT POPULATION

Adults 18 years or older with early-stage (stages IA-IIA, according to the TNM staging system) CTCL (MF) confirmed by histopathological analysis and involving up to 50% body surface area were eligible for the study. Patients with Sezary syndrome, visceral involvement with CTCL, histologically positive lymphadenopathy, or cutaneous tumors were excluded by the early-stage design. Participants were to be free of other illness or infection, to meet laboratory criteria, and to be adequately washed out of topical CTCL therapies for 3 weeks and from systemic CTCL therapies for 4 weeks. Patients were required to use contraception during the trial, and women could not be pregnant or breastfeeding. All patients gave informed consent and met the entry criteria for enrollment except for one, who obtained a waiver for study entry with stage IA disease.

IA disease never progress to a more advanced stage of disease, and the overall survival rate of patients with stage IA disease did not differ from that of control subjects matched for age, sex, and race. Early-stage MF is treated locally because most patients respond to skin-directed therapy adequately and because more aggressive therapy has not been shown to improve survival in this disease. There are a limited number of skin-directed therapies that have efficacy in MF or CTCL. Topical corticosteroids applied to CTCL lesions may be of benefit in patients with limited patch-phase disease, but often they have a limited duration of effective disease control and are succeeded by other therapies. Topical mechlorethamine hydrochloride (nitrogen mustard), topical carmustine (BCNU), electron-beam irradiation, psoralen–UV-A (PUVA), and UV-B all are effective in some patients with MF-type CTCL. However, all patients do not respond to these individual therapies, and cutaneous disease often becomes refractory to specific therapies over time. Phototherapies and radiation therapy can be inconvenient to use. Topical mechlorethamine and, less frequently, topical BCNU may induce hypersensitivity reactions that limit their use. In addition, these therapies all increase the risk of secondary skin cancers. This risk increases with the duration of treatment and also with the number of treatment modalities received. Because adverse effects and loss of therapeutic effectiveness are common problems for patients, additional effective skin-directed therapies are still needed.

RESPONSE CRITERIA

Response was determined by using standard oncology criteria for a clinical complete response (CCR) (100% clear, a complete cutaneous remission) and a partial response (PR) (≥50% but <100% improvement). Response was scored on the 7-point scale of the Physician's Global Assessment (PGA) of clinical condition relative to baseline (Table 1). Clinical significance was defined as a 1-point or greater improvement from baseline in overall severity of all lesions' signs and pruritus, which were graded on 9-point scales (grades 0-8; none, mild, moderate, severe, and very severe, with midpoints between each described grade). Because this was a study of early-stage disease, it was expected that baseline overall disease severity grades were likely to range from grades 2 to 5 (mild to moderate severity). In addition, 3 individual index lesions, selected as being representative of overall disease for each patient, were followed for signs of CTCL using the same 9-point grading scale. The effects of treatment were assessed for plaque elevation, erythema, scaling, and pruritus of lesions. If the patient did not have sufficient disease for 3 index lesions, 2 index lesions were followed (11 patients). Response evaluations were made at least every 4 weeks. The protocol-defined evaluation lasted a minimum of 12 weeks, with provisions for patients to continue treatment if they were benefiting from bexarotene gel.

Standard laboratory tests of blood (ie, chemistries, triglyceride levels, complete blood cell counts, and differential white blood cell counts) and urine (ie, urinalysis), physical examinations, and adverse event (AE) monitoring were used to evaluate patient safety. Blood samples were obtained every 4 weeks to measure the systemic level of bexarotene. Adverse events were coded to preferred terms using the Ligand Pharmaceuticals Inc–modified COSTART (coding symbols for a thesaurus of adverse reaction terms) dictionary. For example, investigators' verbatim AE terms "redness," "irritation," and "erythema" were coded as "rash"; "burning," "stinging," "aches," and "lesion pain" were coded as "pain"; and "itching" and "pruritus" were coded as "pruritus." Treatment-limiting toxic effects were defined as grade 3 or 4 on a 4-point scale for cutaneous irritation and as grade 3 or 4 on the National Cancer Institute common toxicity table for systemic events.

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This article presents the results of a phase 1 and 2 clinical trial of bexarotene gel (Targretin; Ligand Pharmaceuticals Inc, San Diego, Calif) for patients with MF. Retinoids affect gene expression by binding to one or more of the 3 retinoic acid receptors α, β, γ or 3 retinoid X receptors α, β, γ nuclear receptors to form transcription factors. Bexarotene selectively binds retinoid X receptors with high affinity, in contrast to retinoic acid, which binds the 3 nuclear retinoic acid receptors. Selective affinity to retinoid X receptors is believed to give bexarotene different properties from retinoid acid receptor–binding retinoids, such as all-trans-retinoic acid or 13-cis-retinoic acid. Retinoic acid receptor–type retinoids such as isoretinoin and etretinate have demonstrated clinical activity in CTCL, and a retinoid X receptor–selective retinoid may have improved antineoplastic properties. Topical application of bexarotene in gel form was chosen for initial clinical trials in MF because it allowed a high concentration of drug at lesional skin sites while minimizing systemic exposure.

### RESULTS

#### BASELINE CHARACTERISTICS

At 3 study centers, 21, 33, and 13 patients were enrolled, for a total of 67 patients. Participants included 37 men (55%) and 30 women (45%) with a median age of 61 years (range, 30-87 years) and stages IA through IIA MF (and 1 protocol deviation of stage IIB). Fifty-seven patients (85%) were white, 8 (12%) were black, and 2 (3%) were Hispanic. Patient demographics, disease burden, and treatment histories were consistent across all 3 study centers. At baseline, patients had a mean body surface area involved with disease of 11.7% (median, 5.0%; range, 0.1%-50.0%).

There were 41 patients (61%) with stage IA CTCL, 20 (30%) with stage IB, 5 (8%) with stage IIA, and 1 with stage IIB who entered the study under a protocol waiver. Fifty-five patients underwent 1 to 6 therapies before entering this study. Most patients, 36 (54%) of 67, had 1 or more previous local therapies for MF-type CTCL, including topical mechlorethamine (33 patients [49%]), topical corticosteroids (30 patients [45%]), and other skin-directed therapies (PUVA, UV-B, or electron-beam radiotherapy). Nineteen patients (28%) had received systemic (eg, interferon, methotrexate, mechlorethamine, etretinate, isoretinoin, corticosteroids, CHOP [cyclophosphamide, doxorubicin, vincristine sulfate, prednisone], or CMED [cytoxin, methotrexate, etopside, dexamethasone]) and topical therapies, including combined modality therapies. Previous therapies in these patients were often discontinued because of “stable disease,” with no further improvement or relapse after months of treatment. In addition, there were 24 patients recorded as “refractory” to corticosteroids, 13 to meclomethamine, 14 to UV-B or PUVA, 4 to radiation, and 1 to carmustine and 8 as intolerant to meclomethamine, 4 to UV-B or PUVA, 2 to carmustine, 2 to isotretinoin, 2 to methotrexate, and 2 to interferon. Twelve patients (18%) entered the study having undergone no previous therapy for CTCL.

#### SAFETY AND TOLERANCE

Bexarotene gel was well tolerated over a median treatment duration of 315 days (10.5 months) and a maximum ongoing treatment duration of more than 59 months (4.9 years). Sixty-five patients (97%) in these studies had

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### Table 1. Criteria for Response From the Physician’s Global Assessment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Completely clear</td>
<td>No evidence of disease; 100% improvement</td>
</tr>
<tr>
<td>1</td>
<td>Marked improvement</td>
<td>Very obvious clearance (≥90% to &lt;100%); only traces of disease remain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate improvement</td>
<td>Significant improvement (≥50% to &lt;90%); some evidence of disease remains</td>
</tr>
<tr>
<td>3</td>
<td>Slight improvement</td>
<td>Intermediate between marked and mild (≥25% to &lt;50%); half of the disease remains</td>
</tr>
<tr>
<td>4</td>
<td>Any change</td>
<td>Disease has not changed from baseline (10% to −25%)</td>
</tr>
<tr>
<td>5</td>
<td>Condition worse</td>
<td>Disease is worse than at baseline by ≥25%</td>
</tr>
</tbody>
</table>

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### Table 2. Drug-Related Adverse Events (AEs) Occurring With ≥5% Incidence in 67 Patients With Cutaneous T-Cell Lymphoma

<table>
<thead>
<tr>
<th>Preferred Term for AE</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Any Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any related AE†</td>
<td>17 (26)</td>
<td>27 (40)</td>
<td>14 (21)</td>
<td>58 (87)</td>
</tr>
<tr>
<td>Rash</td>
<td>22 (33)</td>
<td>24 (36)</td>
<td>3 (4)</td>
<td>49 (73)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (12)</td>
<td>8 (12)</td>
<td>6 (9)</td>
<td>22 (33)</td>
</tr>
<tr>
<td>Pain</td>
<td>8 (12)</td>
<td>5 (7)</td>
<td>3 (4)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Vesiculobullous rash</td>
<td>2 (3)</td>
<td>0</td>
<td>2 (3)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

*Preferred term coded according to the Ligand Pharmaceuticals Inc–modified COSTART 5 (coding symbols for a thesaurus of adverse reaction terms) dictionary. Patients were counted only once for each preferred term and were classified by the AE with the highest severity.

†Patients were counted for any related AE by the highest-severity AE. Related AEs were those considered at least possibly related by the investigator.
at least 1 AE, and 58 (87%) had a local AE (eg, erythema or irritation) assessed as at least possibly related to treatment (Table 2). Most AEs were mild to moderate and were confined to the cutaneous treatment area. Adverse events at least possibly related to bexarotene use experienced by 5% (3/67) or more of patients were rash, pruritus, pain, vesiculobullous rash, and headache. Adverse events coded as rash could be confused with the signs of CTCL, but the onset of rash after 2 to 6 weeks suggests that investigators could generally distinguish between retinoid irritation and signs of CTCL. For 43 patients who had an initial AE of rash (eg, erythema or irritation) within 100 days of baseline, the median time to onset was 45 days of treatment (range, 8-99 days). Ten other patients had an initial AE of rash beginning 120 to 491 days after onset of treatment. Adverse events coded as rash often continued intermittently or continuously for most of the duration of treatment. Rash was typically a mild, tolerable AE, and 25 patients had it recorded for 100 days or more and a few for as long as 600 days.

Laboratory abnormalities not necessarily related to gel application with an incidence of 5% or greater were observed for glucose levels above or below the reference range in 25 patients (37%), phosphorus levels below normal in 21 (31%), lymphocyte counts below normal in 14 (21%), creatine kinase levels above normal in 7 (11%), bilirubin levels above normal in 4 (6%), and triglyceride concentrations above normal in 3 (5%). Adverse events, detected from abnormal laboratory findings, were recorded for abnormal liver function in 4 patients (6%) and for 1 patient (1%) each for polycythemia, hyperglycemia, albuminuria, and increased creatinine phosphokinase, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase levels (ALT).

Treatment-limiting toxic effects occurred in 16 patients (Table 3). The incidence of application site treatment-limiting toxic effects increased with the concentration of gel being used. With the exception of 1 patient with trigeminal neuralgia, these were all application site events associated with dermal irritation (eg, pain, edema, or rash). The neuralgia of undetermined origin in 1 patient at week 18 of treatment was recorded as a possible treatment-limiting toxic effect before the patient was withdrawn. Serious AEs were reported for 8 patients during the study, but none of these was classified as related to treatment by the investigator or the sponsor. Serious AEs included infections, cardiovascular events, and skin cancers, which are not uncommon for the age and previous treatments of the study population. No deaths were reported during treatment or within 30 days thereafter.

Four patients withdrew from the study because of an AE at least possibly related to treatment. Three of these withdrawals were due to cutaneous conditions associated with treated areas (rash, pruritus, or skin necrosis [leukocytoclastic vasculitis]), and 1 was the patient with trigeminal neuralgia. The withdrawal because of rash occurred at week 20 with 1.0% gel BID in a 72-year-old woman who was using 0.5% gel QD. Withdrawal because of leukoblastic vasculitis occurred at week 10 in a 63-year-old woman who had a PR and was applying 1% gel QD.

### EFFICACY RESULTS

Bexarotene gel produced 50% improvement or more (CCR and PR) in 42 treated patients (63%) based on the PGA of cutaneous disease as the primary end point (Table 4). The 95% confidence interval using the exact method was 50% to 74%. The CCR rate was 21% (14/67) based on patients who fully cleared of cutaneous disease for at least 4 weeks during treatment. An additional 28 patients (42%) had a PR. Of the remaining patients, 14 (21%) had stable disease and only 11 (16%) developed progressive disease during treatment.

A few patients had no previous CTCL therapy and achieved a PGA response rate of 75% (9/12), which was higher than the 67% (24/36) rate for patients who had previously received topical or radiation therapies only and the 47% (9/19) response rate for patients who had previous topical or radiation therapies and systemic therapies (Table 5). Patients who were naive to CTCL therapies had the greatest response rate to bexarotene gel. However, 33 of 42 responding patients (10 of whom had a CCR) underwent previous therapies. Of these 33 responding patients, 22 were refractory or intolerant to 1 (11 patients), 2 (7 patients), or at least 3 (4 patients) previous therapies, including the systemic treatments 13-cis-retinoic acid (2 patients) and methotrexate (1 patient) and the skin-

### Table 3. Treatment-Limiting Toxic Effects (TLTs) by Dose Regimen in 16 Patients With Cutaneous T-Cell Lymphoma*

<table>
<thead>
<tr>
<th>Bexarotene Gel Concentration, %</th>
<th>Any TLT†</th>
<th>Facial edema</th>
<th>Pain</th>
<th>Neuralgia</th>
<th>Skin necrosis‡</th>
<th>Rash</th>
<th>Vesiculobullous rash</th>
<th>Skin ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 (n = 67)</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5 (n = 64)</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.0 (n = 58)</td>
<td>11 (19)</td>
<td>4 (7)</td>
<td>5 (9)</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients.
†Preferred term coded according to the Ligand Pharmaceuticals Inc-modified COSTART 5 (coding symbols for a thesaurus of adverse reaction terms) dictionary. Patients were counted only once for each preferred term and were classified by the adverse event with the highest severity.
‡Reported as leukocytoclastic vasculitis before COSTART coding.

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**Table 4. Response to Bexarotene Gel Treatment According to the Physician’s Global Assessment**

<table>
<thead>
<tr>
<th>Response*</th>
<th>Patients, No.</th>
<th>Response Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical complete response (100% clearing)</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Partial response (≥50%-99% clearing)</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>Subtotal</td>
<td>42</td>
<td>63</td>
</tr>
<tr>
<td>Stable disease (&lt;50% clearing)</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Progressive disease (≥25% worse)</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

*Confirmed by at least 2 evaluations 4 or more study weeks apart.
directed therapies corticosteroids (12 patients), mechlorethamine (13 patients), UV-B (3 patients), PUVA (4 patients), radiation (2 patients), and Carmustine (1 patient).

Evaluation of overall severity of disease, which graded the severity of cutaneous signs of disease and area of involvement of CTCL, was a secondary end point. By overall severity, the response rate was 51% (34/67), as assessed by a 1-grade or more improvement on or before 16 weeks of treatment relative to baseline. At baseline, there was a median grade in overall severity of 1.67 (range, 0.33-4.33) for all signs and symptoms, so a 1-grade improvement was substantial (≥50% on average). The 95% confidence interval for this response using the exact method was 38% to 63%. The response rate by overall severity was more stringent because it was restricted to the initial 16 weeks of therapy and the PGA response end point could occur anytime during treatment. However, the confidence intervals of the 2 end points for response were similar.

**Figure 1** shows a PR to treatment with bexarotene gel at week 4 of therapy for a 50-year-old woman with stage IB CTCL. Her right shoulder is shown at baseline (day 1, before treatment) (Figure 1A) and at week 4 (Figure 1B). She achieved a PR at week 6 and relapsed at week 69.

The Kaplan-Meier projected time to onset of response (≥50% improvement) for all patients was a median of 20.1 weeks (range, 4.0-86.0 weeks). Of the 42 responding patients, 17 (40%) relapsed from CCR or PR to a lower response criteria (stable or progressive disease) during treatment, but 13 (31%) responded again with continued gel treatment. Using Kaplan-Meier analysis, the projected median duration of response by PGA criteria from the start of gel therapy to the time of relapse was 99 weeks (range, 12-99 weeks), and the median durability of response from onset of response to time of relapse was 61.1 weeks.

Eleven of the 42 patients who achieved a confirmed response reverted to stable disease on treatment, but 7 of these 11 patients again had a PR, and 2 had a CCR. All 11 of these patients were being treated for longer than 8 months at relapse, with a median treatment duration of 73 weeks (range, 34-172 weeks). Only 4 patients terminated treatment with confirmed stable disease after a PR. For 14 patients who achieved a CCR, the median duration of remission was 8 weeks (range, 3-62 weeks). Six patients responded to bexarotene gel with a confirmed CCR more than once, with periods of PR only (4 patients) or stable disease and PR (2 patients) between CCR remissions. Six patients remained in CCR at termination of treatment. After treatment was discontinued, data on relapse from response criteria were not collected.

The cutaneous signs of erythema, scaling, and plaque elevation were typically mild to moderate at baseline. They were evaluated on 3 index lesions for 56 patients and on 2 index lesions for 11 patients who had limited disease. On a scale from 0 to 8 (none, mild, moderate, severe, and very severe, with midpoints between defined grades), mean grades at baseline were 1.7 for scaling (range, 0.6-4.0), 2.8 for erythema (range, 0-5.7), and 4.6 for pruritus (range, 0-6.7). Sixty-five percent of patients had signs present at baseline for erythema, 57 for scaling, 42 for plaque elevation, and 25 for pruritus. Clinical improvement was observed in each of these signs and symptoms for the index lesions selected on each patient at baseline. Improvement was rapid for plaque elevation and scaling during the first 8 weeks of treatment but was more gradual for erythema and pruritus (**Figure 2**). The mean grade of all patients’ index lesions at week 8 as a percentage of the baseline grade was 43% for scaling (change in mean from grade 1.7 to grade 0.73; P = .001), 30% for plaque elevation (grade 1.1 to grade 0.34; P = .001), 79% for erythema (grade 2.8 to grade 2.21; P = .004), and 63% for pruritus (grade 1.1 to grade 0.69; P = .12).

**Table 5. Previous Therapy and Response Rate in 67 Patients With Cutaneous T-Cell Lymphoma**

<table>
<thead>
<tr>
<th>Previous Therapy†</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12 (43)</td>
</tr>
<tr>
<td>Topical only</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Topical and systemic</td>
<td>19 (16)</td>
</tr>
</tbody>
</table>

*CCR indicates complete clinical response; PR, partial response.
†Responding patients were refractory or intolerant to systemic 13-cis-retinoic acid (n = 5), interferon (n = 4), methotrexate (n = 2), corticosteroids (n = 2), skin-directed corticosteroids (n = 19), mechlorethamine (n = 16), UV-B (n = 6), psoralen-UV-A (n = 5), radiation (n = 3), and Carmustine (n = 1).

**Figure 1.** Right shoulder lesion on a 50-year-old woman with stage IB cutaneous T-cell lymphoma (25% body surface area) for more than 5 years. A, Baseline (day 1, before treatment). B, Partial response at week 4 of treatment with bexarotene.
Forty-nine study patients were enrolled on the initial dose escalation regimen from 0.1% QD to 1.0% QID. For the last 18 patients, a protocol amendment changed the treatment regimen to escalate stepwise from an initial dose of 1.0% every other day to 1.0% QID. On the initial dose escalation regimen, most patients (37 of 49) reached and tolerated treatment with the 1.0% gel concentration for at least 4 weeks, with minor adjustments for irritation. Three patients did not tolerate 1.0% gel for 4 weeks and were reduced in dose, and 9 patients were never treated with the 1.0% gel and remained at 0.5% (n = 5) or 0.1% (n = 4). Five of these 9 patients were studied for 20 weeks or less. Median treatment duration with bexarotene gel was 10.5 months. Thirty-five patients remained in the study with only bexarotene gel therapy for more than 1 year, 20 remained for more than 2 years, 10 remained for more than 3 years, and 3 have been studied for more than 4 years. Some patients continued therapy with commercial bexarotene gel, and several of these have been treated for 5 years.

Patients responded at all concentrations of bexarotene gel, and the response rate increased in relation to the concentration and frequency of the dose regimen administered before response (Table 6). Eighteen patients did not have the opportunity to respond at the 0.01% or 0.5% gel exposures because a protocol amendment restricted them to 1.0% gel. For 22 (52%) of 42 responding patients, the initial response was confirmed after beginning 1.0% gel treatment, in contrast to 13 patients (31%) who responded to 0.5% gel and 7 (17%) to 0.1% gel. Three responses at 0.1% bexarotene gel occurred at weeks 33, 33, and 86 of treatment, later than observed for the higher gel concentrations of bexarotene gel. The 4 other patients responded at 0.1% gel during the biweekly dose escalation scheme of the protocol. Patients who eventually attained CCR were applying 1.0% gel BID at or just before total clearing except for 1 patient using 0.5% BID and 1 patient using 0.1% QD. These data suggest a correlation of response with the intensity of bexarotene gel exposure.

Plasma levels of bexarotene were evaluated from 66 patients every 2 to 4 weeks. Forty-two (64%) of 66 patients had at least 1 blood sample quantifiable for bexarotene (1 ng/mL limit of detection). Despite long-term study treatment, bexarotene was quantifiable in only 169 (21%) of 807 postdose samples. It was present at low serum levels (<5 ng/mL) in 129 (16%) of samples (quantifiable serum concentrations ranged from 1-28 ng/mL). Only 3 samples were found to have a bexarotene concentration greater than 20 ng/mL. Bexarotene was not detected in 638 (79%) of postdose samples. The level of systemic exposure detected in plasma seemed to be associated with the body surface area treated with bexarotene gel. This is consistent with its short plasma half-life (2-7 hours) as determined by orally administered bexarotene capsules.15

**Table 6. Dose Regimen of Bexarotene Gel at Onset of Response**

<table>
<thead>
<tr>
<th>Bexarotene Gel Regimen</th>
<th>Responding Patients, No. (%) (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0% BID</td>
<td>14 (33)</td>
</tr>
<tr>
<td>1.0% QOD-QD</td>
<td>8 (19)</td>
</tr>
<tr>
<td>0.5% BID</td>
<td>9 (21)</td>
</tr>
<tr>
<td>0.5% QD</td>
<td>4 (10)</td>
</tr>
<tr>
<td>0.1% QD or BID</td>
<td>7 (17)</td>
</tr>
</tbody>
</table>

*If the patient was suspended from treatment at the time of response, the last dose regimen before response was used. BID indicates twice daily; QOD, every other day; and QD, once daily.

**COMMENT**

This phase 1 and 2 trial demonstrated the clinical benefit of using bexarotene gel in patients with early-stage MF-type CTCL. Bexarotene is a novel retinoid X receptor-selective ligand whose exact mechanism of action in CTCL is not yet defined. It may have a direct effect on transformed T cells of CTCL, or it may work indirectly, such as through cytokine modulation or receptor induction in the CTCL skin lesions.16 Pivotal studies with oral bexarotene capsules in patients with CTCL at an initial dose of 300 mg/m² per day had a response rate of 54% in early-stage disease and of 45% in advanced disease.17,18 When applied topically, bexarotene gel may lead to a local concentration of drug in cutaneous lesions higher than that induced by oral administration and with negligible systemic exposure for patients with early-stage disease.

A placebo control group was not part of this phase 1 and 2 study. The spontaneous remission rate is assumed to be low (<10%), especially considering the number of patients who had failed previous therapies. Spontaneous remission rates for CTCL or placebo-controlled trials from which they could be projected have not been published, to our knowledge. However, the safety of bexarotene gel and its potential therapeutic utility in CTCL were demonstrated in this study. Of 14 patients (21%) who achieved a CCR (100% clear) in this trial, 10 underwent previous therapies for CTCL that were unsatisfactory because of incomplete response, intolerance, or relapse. By the overall disease severity end point, 51% of patients responded within 16 weeks of beginning treatment; by the PGA, 63% of patients responded at any time during treatment. These response rates suggest that bexarotene gel can be considered a therapeutic alternative in early-stage disease and can also be used as adjunctive therapy in recalcitrant or relapsed lesions.
Bexarotene gel had a generally tolerable safety profile. Adverse effects from using bexarotene gel were generally restricted to the site of application. Adverse events deemed at least possibly related to therapy were rash or irritation, pruritus, pain, and headache. These events were temporary and easily managed. Some patients developed an asymptomatic “retinoid erythema” in treated areas that was coded to rash. For significant irritation, a decrease in application frequency or a temporary suspension of treatment was instituted. Treatment-limiting toxic effects were generally related to the dose regimen of the gel and manifested as cutaneous irritation. In practice, these events were self-limiting in severity, as patients tended to limit their exposure to the application frequency that was within tolerance. Application frequency alone was used for dose adjustments in patients whose treatment was limited to 1.0% gel. Eleven patients with 20% to 50% body involvement responded to treatment, demonstrating that irritation on skin lesions can be safely managed for patients with large areas of MF. Only 2 patients withdrew from the study because of cutaneous irritation related to treatment; 2 others withdrew because of leukocytoclastic vasculitis and trigeminal neuralgia.

The PGA used as the primary end point in this study was supported by the overall severity of disease score, and both 95% confidence intervals were similar. The overall severity was a grade for signs of disease from all treated lesions (both index and nonindex). The overall severity end point produced a 51% response rate at 16 weeks of therapy (a protocol measure of clinical significance) compared with a response rate of 39% by PGA at 16 weeks that increased to 63% with longer treatment. The PGA is a reliable end point that has also been used in trials of other dermatological disorders, such as psoriasis and atopic dermatitis, which also have clinical presentations that are difficult to quantitate.

The improvement in patients from the start of therapy to the time of response can be seen in the decrease in the mean grades for the individual signs of disease over time, including erythema, scaling, and plaque elevation. Scaling and plaque elevation were much improved by 8 weeks in most patients. The erythema grade did not decrease as much as or as rapidly as the other signs, at least partly because bexarotene commonly induced a retinoid erythema at the site of application, which could be difficult to differentiate during therapy from erythema due to the disease. Responses were generally stable during treatment. Only 4 of the 28 patients who achieved a PR left the study with a confirmed relapse to stable disease. Five other patients who relapsed from PR responded again with continued treatment. The treated lesions were well controlled by bexarotene gel, and relapse with subsequent responses were sometimes due to new lesions in areas not being treated with gel. The subset of patients who relapsed from response was treated for 34 to 172 weeks (0.65–3.0 years).

The complete skin remissions (CCRs) that occurred in 14 patients lasted up to 77 weeks (median, 11 weeks) from the start of remission to the time of relapse. In 5 of these patients, a CCR was achieved several times during treatment. This reflected the systemic nature of CTCL and the formation of new skin lesions. When patients who achieved a CCR relapsed, it was primarily to a PR relative to baseline, and none left the study without being in response (≥50% improvement compared with baseline). These data indicate that continued treatment with bexarotene gel may be warranted for patients who develop a few new lesions or who have a temporary decrease in response, as patients are likely to achieve their previous maximum response again. Bexarotene gel can be considered for control of limited cutaneous CTCL patches or plaques for extended periods. Fifteen patients up to 86 years of age had longer response durations than the study-determined median of 99 weeks and had been treated with bexarotene gel for 2 to more than 4 years.

Patients responded to bexarotene gel whether or not they had previous therapies for CTCL and even if they were resistant to previously used topical or systemic agents. Twelve patients (18%) had bexarotene gel as the first CTCL therapy, and 4 of these achieved a CCR. Another 5 of these treatment-naive patients had a PR, for an overall response rate of 75% (9/12). This rate was higher than for patients who had previous topical therapies (67%) and for patients with previous topical and systemic therapies (47%). Additional study may demonstrate that bexarotene gel is effective as an initial therapy for CTCL and is useful in patients who have failed standard skin-directed therapies. For patients who had experienced resistance or intolerance to previous topical and systemic therapies, 47% responded to bexarotene gel.

Skin-directed therapies such as UV-B phototherapy, PUVA, electron-beam irradiation, topical mechlorethamine, topical corticosteroids, and topical Carmustine have documented efficacy in early-stage CTCL. These may be delivered to whole skin, but it is not uncommon in early-stage CTCL to apply topical therapies such as BCNU, mechlorethamine ointment, or corticosteroids as lesion-directed therapy. Lesion-directed therapy may be used in patients with stage IA disease who are not progressing or to minimize treatment toxic effects in patients who have an increased risk of secondary skin cancers from multiple treatments or who have considerable photodamage. Topical corticosteroids are used for lesion-directed therapy and are often the initial treatment for CTCL. Topical corticosteroids may initially work well but in many patients lose efficacy after months or years of therapy, and an alternative treatment is needed. Bexarotene gel was tested as a lesion-directed therapy and may serve as an alternative to other lesion-directed therapies.

There are several early-stage CTCL therapies with established therapeutic profiles. Up to 83% of patients with stage I limited patch disease responded to UV-B, with a response duration up to 22 months. Psoralen–UV-A has a response rate of 60% to 90% in early-stage CTCL for 20 months or more, and topical mechlorethamine used on the whole body has a rate of 50% to 80% with a median duration of response of 8 to 12 months or more. Total skin electron-beam irradiation had a response rate of more than 80% and in stage IA is believed to produce occasional cures. Despite these response rates, there are limitations for all therapies for CTCL due to patient treatment histories, disabilities, and age. For such reasons,
patients need a variety of alternative treatments used in sequence or in combination for particular situations. Patients in the present study had discontinued previous therapies for lack of response or intolerance to topical corticosteroids, topical mechlorethamine, topical carmustine, PUVA, UV-B, and electron beam but then responded to bexarotene gel, suggesting that the gel can also serve as an additional treatment option.

The risk-benefit profile of bexarotene gel seems to support this agent as a therapeutic alternative given the chronic nature of CTCL and the limitations of all therapies in early-stage disease. The main adverse effect of topical bexarotene, local redness and irritation, is self-limiting and easily managed by brief suspensions from treatment, decreases in application frequency, or concomitant use of moisturizers. The level of systemic exposure from topical bexarotene gel is low,15 and no significant sensitization potential has been identified. As a retinoid gel, pregnant women should not use it. Women of childbearing potential must use reliable contraceptives with bexarotene therapy. Bexarotene gel is approved by the Food and Drug Administration for the topical treatment of cutaneous lesions in patients with CTCL (stages IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.

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REFERENCES

general patients have been described as having an IgA-predominant response. There are no previously well-documented cases of IgM EBA. Bullous eruptions resembling bullous pemphigoid or EBA have rarely been seen in patients with IgM gammopathies, but no specific antigenic targets have been determined.1-7 It is hypothesized that these patients produce a monoclonal IgM that cross-reacts with a component of the skin. Our patient had no evidence of an IgM gammopathy at presentation or in subsequent follow-up.

Isotype switching is a complex process that is dependent on signals from CD4+ T helper cells, cytokines, and the CD40 ligand. Whether our patient’s IgM response reflects a different pathogenic stimulus for autoantibody formation or an atypical response by his immune system remains to be determined.

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