Incidence of spontaneous remission in patients with CD25-positive mycosis fungoides/Sézary syndrome receiving placebo

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Background: Spontaneous remission is recognized in mycosis fungoides (MF) and Sézary syndrome (SS).

Objective: We analyzed the outcome of 44 patients with previously treated CD25-positive (CD25+), recurrent/persistent MF/SS randomly assigned to receive placebo as part of a phase III trial.

Methods: This trial investigated the efficacy and safety of two doses of denileukin diftitox in patients with MF/SS who had received up to 3 prior therapies. The primary end point was overall response rate. Multivariate regression analyses were used to assess the relationship between baseline covariates and clinical outcomes.

Results: The overall response rate was 15.9% for placebo recipients (complete response: 2.3%; partial response: 13.6%), reflecting the baseline rate of disease remission that can be expected in a clinical trial. The median progression-free survival (PFS) in the placebo arm was moderately short at 4.4 months compared with the active-agent arm but important to consider in the context of recent single-arm phase II studies of other therapies for MF/SS that report PFS of approximately 6 months. Multivariate analyses identified no significant effects of any baseline factors on either overall response rate or PFS, although there was a trend toward poorer PFS with advanced age. Because sepsis occurred significantly more often in the placebo arm versus the active-treatment arm, the role of antibiotics in causing remission cannot be discounted (6.8% vs 0%; $P < .05$).

Limitations: This study had a relatively small sample size, yielding a wide 95% confidence interval.

Conclusion: The results may serve as a useful comparator for other active-treatment studies of MF/SS that lack a placebo-control arm. (J Am Acad Dermatol 2012;67:867-75.)

Key words: cutaneous T-cell lymphoma; denileukin diftitox; lymphoma; mycosis fungoides; placebo; Sézary syndrome; spontaneous remission.

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Cutaneous T-cell lymphomas (CTCL) are rare, extranodal types of non-Hodgkin lymphoma characterized by accumulation of malignant T lymphocytes in the skin.[1,2] The most common variants include mycosis fungoides (MF)[2] and Sézary syndrome (SS).[3] Although MF features characteristic patches, plaques, and tumors arising in the skin and a fairly indolent course, SS is an aggressive leukemic variant featuring diffuse erythroderma with circulating malignant T lymphocytes.[2] MF accounts for approximately 60% of all new CTCL cases, but SS only comprises about 5%.[3]

The CTCL annual incidence is approximately 7.7 cases per 1 million individuals.[4] The Surveillance, Epidemiology, and End Results database showed that the incidence of CTCL in the United States increased from 2.8 to 9.6 person-years between 1973 and 2002, so CTCL now comprises 3.9% of all non-Hodgkin lymphomas.

CAPSULE SUMMARY

- Spontaneous remission occurs in mycosis fungoides and Sézary syndrome.
- In 44 patients with previously treated CD25+ mycosis fungoides/Sézary syndrome who received placebo in a phase III, randomized, placebo-controlled trial of denileukin diftitox, overall response rate was 15.9%, reflecting spontaneous remission, and progression-free survival was 4.4 months.
- These results may serve as a useful comparator for other studies of mycosis fungoides/Sézary syndrome.

L4389-11, the largest randomized, double-blind, placebo-controlled, phase III trial in CTCL to date, was recently completed.[5] In this trial, two doses (9 or 18 μg/kg/d for 5 days every 21 days) of denileukin diftitox (DD) were compared with placebo in 144 patients with stage IA to III disease who had received up to 3 prior therapies.[5] DD is approved for patients with relapsed CTCL that expresses CD25 on 20% or more of T cells in biopsied skin lesions analyzed by immunohistochemistry.[5] Patients who were not CD25 positive (CD25+) were excluded. The findings showed that DD is effective in early- and advanced-stage CD25+ MF/SS that progressed or was refractory to several prior therapies, yielding an overall response rate (ORR) of 44% versus 16% for placebo and a median progression-free survival (PFS) of 971 days in those receiving DD (18 μg/kg/d).[5]

The response rate of 16% in the placebo arm of study L4389-11 was surprisingly high. Considering the rarity of MF/SS, the large number of patients in study L4389-11, and close prospective patient follow-up, we examined the placebo arm in detail to determine what may have contributed to the high "spontaneous" response rate. Here, we analyze initial disease characteristics to determine if any baseline factors were predictive of placebo response. Because it is well recognized that staphylococcal colonization or infection may worsen MF/SS symptoms,[6,7] we were particularly interested in responses possibly associated with treatment of coexistent infection.

METHODS

Study population

Adults with histopathologically confirmed stage IA to III MF/SS, CD25+ expression (defined as detectable CD25 on $\geq$ 20% of T cells in biopsied skin lesions by immunohistochemistry), evaluable disease in skin or blood, and life expectancy 12 months or longer were eligible to participate. Patients had to have Eastern Cooperative Oncology Group performance status of 0 or 1, received up to 3 prior treatments (regardless of number of courses or repeated treatment), only one prior systemic CTCL regimen, and no prior DD treatment. Patients were excluded if they had involvement of bone marrow (>20% circulating abnormal lymphocytes), liver, or spleen; biopsy-confirmed lymph node status LN3 or higher (large cluster of cells in a dermatopathic node indicating lymphoma involvement); or presence of high-grade or large-cell, poorly differentiated tumors.

Study design

Details of the study design of trial L4389-11 were previously reported.[5] Briefly, patients were randomly assigned to DD at 9 μg/kg/d, DD at 18 μg/kg/d, or placebo. Randomization was stratified by disease stage ($\leq$ IIA or $\geq$ IIB). Patients received up to 8 courses of treatment every 21 days for approximately 6 months. Each course was planned to comprise a 30-minute intravenous infusion of DD or placebo on days 1 through 5 on an outpatient basis, with courses repeated every 21 days as tolerated. Patients were ineligible for further participation if they experienced a dose-limiting toxicity or progressive disease (PD) or if they received another anticancer treatment.

Patients received premedication with acetaminophen (325-650 mg) and antihistamine 30 to 60 minutes before each infusion. These medications were continued during and after the dosing period, as clinically indicated. Dose interruptions lasting up to 7 days were permitted for patients developing grade 2 or 3 toxicities. Patients experiencing dose-limiting toxicities could delay the next treatment