Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

Cancer Therapy: Clinical

Clinical Cancer Research

Long-term Outcomes of 1,263 Patients with Mycosis Fungoides and Sézary Syndrome from 1982 to 2009

Rakhshandra Talpur[1], Lotika Singh[1], Seema Daulat[1], Ping Liu[2], Sarah Seyfer[1], Tanya Trynosky[1], Wei Wei[2], and Madeleine Duvic[1]

Abstract

Purpose: The purpose of this prospectively collected single center study cohort of 1,263 patients with mycosis fungoides (MF)/Sézary syndrome (SS) is to evaluate the significance of stage and risk of disease progression from initial presentation and to examine other prognostic factors.

Patients and Methods: The prognostic variables effecting overall survival (OS) were examined in a unique prospective cohort of 1,263 patients with MF and SS seen by one investigator at MD Anderson Cancer Center (Houston, TX) from 1982 to 2009. Kaplan–Meier estimates were used to determine median OS, progression-free survival (PFS), and disease-specific survival (DSS). Cox proportional hazards regression model assessed prognostic factors.

Results: Mean age at diagnosis was 55.33 years. Early mycosis fungoides (stage IA–IIA) represented 71.5% (903 of 1,263) and advanced (stage IIB–IVB) 28.5% (360 of 1,263) patients. Progression to a higher stage occurred in 147 patients (11.6%) of whom 112 (12%) were early and 35 (9.7%) advanced. Death from disease occurred in 102 of 1,263 (8.1%) patients. Median OS was 24.44 years, PFS was 16 years, and median DSS was not reached. OS and PFS were significantly better for early-stage patients with patches (T1a/T2a) than with patches/plaques (T1b/T2b). The PFS analyzed in 1,241 patients found that only 337 (27.2%) had disease progression or had died from disease. Risk factors associated with progression or deaths were advanced age, plaque stage, lactate dehydrogenase (LDH) level, and tumor area.

Conclusions: Improved outcome of MF/SS, reflected by OS and PFS for all stages, may result from earlier diagnosis, new therapies, and aggressive treatment of infections. *Clin Cancer Res; 18(18); 5051–60. ©2012 AACR.*

Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of nonHodgkin lymphomas characterized by skin infiltration of neoplastic T lymphocytes. Mycosis fungoides (MF), and its leukemic variant Sézary syndrome (SS), are characterized by a monoclonal proliferation of CD4+/CD45R0+ peripheral or central memory T cells, respectively, as well as loss of mature T-cell antigens (i.e., CD3, 5, 7; ref. 1). Incidence rates for all CTCLs in the U.S. population have been estimated at 7.7 per 1,000,000 person-years (2), similar to 6.4 per 1,000,000 previously reported by a Surveillance, Epidemiology and End Results (SEER)-based study using the data from the original 9 registries analyzing 4,783 cases of CTCLs from 1973 to 2002 (3). MF is the most common primary cutaneous lymphoma, with incidence rate of 4.1 per 1,000,000 person-years with a male to female incidence rate of 1.66 (2). With the exception of patients with stage IA, limited patch, and/or plaque MF (T1), the overall survival (OS) of patients with MF is inferior to age-, sex-, and race-matched control populations (4–10). Published risk factors for survival in MF and SS include demographics, skin T-stage, presence of extracutaneous disease, such as lymphadenopathy and peripheral blood involvement (4–16), large cell transformation (LCT; refs. 17, 18), as well as increased levels of serum lactate dehydrogenase (LDH), β_2-microglobulin, eosinophilia, and soluble interleukin 2 receptor (19).

Long-term outcomes of the Stanford cohort of 525 patients with CTCLs were reported by Kim and colleagues in 2003. They found a median OS of 10 years and survival equal to age-matched controls in stage IA MF (9). Significant blood involvement (>1,000 SS cells/μL) was B1 but is now B2 in the most recent classification system (20). Thirty-five Stanford patients with B1 or B2 blood involvement had a median survival of only 3.0 years at a time when combined immunomodulatory treatment was being adopted as

Authors'Affiliations: Departments of [1]Dermatology and [2]Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas

Prior presentations: The work was presented in part at the First World Congress of Cutaneous Lymphomas in Chicago, IL, September 22–25, 2010.

Corresponding Author: Madeleine Duvic, Department of Dermatology, MD Anderson Cancer Center, 1400 Pressler – Unit 1452, Houston, TX 77027. Phone: 713-745-4615; Fax: 713-745-3597; E-mail: mduvic@mdanderson.org

doi: 10.1158/1078-0432.CCR-12-0604

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

Translational Relevance

Cutaneous T-cell lymphomas (CTCL), although rare, have great morbidity and may be misdiagnosed or overtreated by clinicians who are unfamiliar with these entities. This is the largest American cohort of patients with CTCLs–mycosis fungoides (MF) and Sézary syndrome (SS) studied for prognostic markers, many of whom were on clinical trials. We report survival advantage for patch as compared with plaque MF involvement and for the number of abnormal circulating cells. CD25+ CD30 expression did not affect the overall survival (OS), whereas patients with poikiloderma or with lymphomatoid papulosis, a CD30 lymphoproliferative disorder, had a significant survival advantage ($P = 0.02$). There is much longer OS than reported for the entire cohort and for patients with SS. This suggests that earlier diagnosis and use of new therapies are having a beneficial effect on patient outcomes. This article should be of great interest to dermatologists and oncologists treating CTCLs.

first-line therapy for patients with SS (21). In an earlier analysis, in patients thus treated (21), we found a median OS of 7.6 years for patients with erythrodermic CTCLs with less than 1,000 SS cells/μL at baseline, 5.4 years for SS patients with hematology stage H3 or B2 (SS counts >1,000 and <10,000 cells/μL), and only 2.4 years for patients at stage H4 (>10,000 SS cells/μL; ref. 16).

The study conducted by Agar and colleagues (10) published a British cohort of 1,502 patients with long-term follow-up of 29 years to validate the International Society for Cutaneous Lymphomas (ISCL) European Organization for Research and Treatment of Cancer (EORTC) revision of MF/SS staging system (20). In their recent study, early skin stage (T1/T2) was subclassified into either patches (T1a or T2a) or a combination of patches and plaques (T1b or T2b). Survival with or without lymph node and blood involvement were also examined in advanced patients (Table 1; ref. 20).

The purpose of this prospectively collected, single center study cohort of MF/SS 1,263 patients was to evaluate the significance of stage and risk of disease progression from initial presentation, as well as to examine other prognostic factors. We also compare our findings with the proposed ISCL/EORTC staging criteria and risk factors. OS, disease-specific survival (DSS), and progression-free survival (PFS) are assessed using univariate and multivariate analysis, similar to Agar and colleagues (10).

Materials and Methods

Patient selection and staging

A prospective laboratory protocol and consent, approved by MD Anderson Institutional Review Board (Houston, TX), allowed us to create a CTCLs patient database including DNA and sera samples. Permission was later granted to conduct a retrospective analysis of 1,500 patients with CTCLs staged and followed at MD Anderson Cancer Center (MDACC) from 1982 to 2009. Data evaluated included diagnostic skin biopsy with T-cell receptor gene analysis from skin ($n = 614$) by polymerase chain amplification and immunohistochemistry for CD30 ($n = 452$) and CD25 ($n = 513$) expression.

Tissue samples and blood at baseline were studied in real time for staging purposes. DNA extracted from paraffin-embedded tissue blocks was subjected to polymerase chain amplification using primers and conditions as previously described by Vega and colleagues (22). As a control for the DNA sample, β-hemoglobin was amplified for comparison. Initially, manual Sézary cell counts were determined by a hematopathologist and later abandoned on the basis of our published study correlating SS cell numbers with CD4+CD26− absolute counts determined by flow cytometry. Multicolor flow cytometry was used to quantitate numbers of CD3+CD4+, CD3+CD8+, CD3+CD7−, and CD4+CD26− for each patient (23). Immunohistochemical analysis of V β-usage was conducted on aberrant T-cell clones by flow cytometry (22).

T-cell receptor β- and γ-gene rearrangements in peripheral blood were assessed by multiplex PCR using a 2-tube multicolor system, capillary electrophoresis, and BIOMED-2 primers (22). We considered significant blood involvement or B2 as more than 1,000 cells/μL or more than 35% CD4+CD26− cells with a clonal population noted on the scattergram. The B0/B1/B2 classification system, which was first used by us in the early 1990s, was later also adopted by the ISCL/EORTC classification described by Olsen and colleagues (20). The classification of blood involvement is B0 <500 Sézary cells/μL; B1 >500 and <1,000 cells/μL; and B2 >1,000 cells/μL or >35% of lymphocytes as CD4+CD26− or CD4+CD7− cells. Patients classified as SS were required to have 80% or more erythroderma as well as B2 (>1,000 atypical circulating cells), and evidence of a peripheral T-cell clone. One hundred and eighty-six patients were confirmed to have SS on the basis of immunohistochemical detection by flow cytometry of peripheral blood samples and molecular assessment of the T-cell receptor at presentation. All patients with SS were treated upfront with immunomodulatory therapy including photopheresis plus biologic response modifiers (21).

Patients with more than 1.5 cm palpable peripheral lymphadenopathy underwent fine needle aspiration or excisional lymph node biopsy for immunohistochemistry and molecular T cell receptor analysis as described earlier. We used the updated ISCL/EORTC classification (20) for lymph nodes: N1 (dermatopathic lymphadenopathy), N2 (dermatopathic lymphadenopathy with early involvement by MF), N3 (partial effacement of LN architecture, many atypical cerebriform mononuclear cells), and N4 (complete effacement).

All patients had an automated total white blood cell (WBC) counts, serum LDH levels ($n = 1,148$), and β_2-microglobulin levels ($n = 834$) at baseline. When indicated by stage >IIA, patients underwent additional staging

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

Table 1. Comparison of OS for reported factors in large MF cohort studies

Characteristics	Long-term outcome of 525 patients (Kim and colleagues; 9)	Validation of ISCL/EORTC. 1,502 patients (Agar and colleagues; 10)	MDACC study of 1,263 MF/SS patients
Time duration	1958–1999	1980–2009	1982–2009
Mycosis fungoides (*n*)	490	1,398	1,062
Sézary syndrome (*n*)	35	104	186
Male (*n*)	330	933	663
Median OS	10 y	13.4 y	20.7 y
Female (*n*)	195	569	585
Median OS	13.5 y	24.1 y	32.0 y
T classification			
T1 (*n*)	159	443	521
Median OS	Not reached	35.5 years	Not reached
T2 (*n*)	192	628	395
Median OS	12.1 y	21.5 y	26.26 y
T3 (*n*)	96	182	136
Median OS	3.3 y	4.1 y	5.96 y
T4 (*n*)	78	234	188
Median OS	4 y	3.9 y	5.00 y
Folliculotropic MF (*n*)		189	44
Median OS		12.2 y	Not reached
Poikiloderma		168	63
Median OS		20.1 y	Not reached
Hypopigmented MF (*n*)		51	54
Median OS		Not reached	32.04 y
Lyp and MF (*n*)		74	45
Median OS		Not reached	Not reached
B0 (*n*)	490	1327	1042
Median OS	12.3 y	24.5 y	29.28 y
B1 (*n*)	35	71	13
Median OS	3 y	3.2 y	Not reached
B2 (*n*)	0	104	186
Median OS		3.1 y	4.64 y
N0 (*n*)	345	1,220	1,112
Median OS	17.4 y	22.8 y	26.26 y
N1 (*n*)	147	87	55
Median OS	6.5 y	5.2 y	16.91 y
N2 (*n*)		8	28
Median OS		1.1 y	5.43 y
N3 (*n*)	33	40	18
Median OS	1.7 y	2 y	6.13 y
N4 (*n*)			33
Median OS			2.85 y
Extracutaneous (*n*)	77	13	70
Median OS	1.1 y	1.4 y	4.42 y

evaluation, including bone-marrow biopsy and imaging studies (computerized tomography scans or positron emission tomography/computerized tomography). Suspected involvement of any visceral sites was confirmed with biopsy whenever possible.

Clinical features evaluated at diagnosis included T-stage as body surface area involved with patches alone, patches and plaques, and plaques alone, presence of histologically confirmed folliculotropic MF, poikiloderma, hypopigmentation, papules of lymphomatoid papulosis, and tumors with or without LCT in skin and lymph nodes. LCT was defined as more than 25% of atypical lymphocytes with nuclei more than 4 times normal size (17). The T-staging system remained constant throughout the study time, although determination of extent of skin lesions by body surface area was later adopted with weighting factors as the

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

modified skin weighted assessment tool. Tumors were evaluated for risk as solitary versus multiple, localized or regional, and for presence or absence of histologic LCT.

Patients diagnosed elsewhere and referred to MDACC were included in the study if baseline diagnostic biopsy for MF or SS counts were available, or if the patient was untreated before presentation. The dates for last follow-up and cause of death were confirmed from the clinical records, and patients' families and physicians were queried with regard to the cause of death whenever possible. The MD Anderson tumor registry was helpful in routinely determining survival and disease status in 100 patients who did not return regularly to the clinic.

Statistical analysis

We used the methods of Kaplan–Meier ([24]) to estimate the median OS, DSS, and PFS. For the analysis of OS, death was counted as an event. For the analysis of DSS, MF-related death was considered as an event. For the analysis of PFS, first disease progression or MF-related death was considered as event. Cox proportional hazards regression model (25) was used to test the statistical significance of potential prognostic factors for OS, DSS, and PFS. The Cox modeling was done in a univariate fashion. From this model, we estimated the HR for each potential prognostic factor with a 95% confidence interval (CI).

All potential prognostic factors with a P value <0.10 from the univariate analysis were then included in a saturated model, and backward elimination was used to remove factors from the model on the basis of the likelihood ratio test in the multiple regression analysis. All analyses were conducted using SAS 9.2 by SAS Institute (Cary, NC).

Results

Patient characteristics

Clinical characteristics, stage, median survival, OS/DSS, and PFS are summarized in Tables 1 and 2. Mean age at diagnosis was 55.33 years (range 8–91 years). The majority of patients (73.4%) were Caucasian and the remainder were of African American (12.9%) or Hispanic descent (10.9%). Unexpectedly, the male to female ratio was almost equal at 1.1:1. Patients with early-stage (IA–IIA) MF ($n = 903$) represented 71.5% of all patients with 447 (49.5%) females and 456 (50.5%) males. Of note, in advanced-stage patients (IIB–IVB; $n = 360$) representing 28.5% of all patients, 145 (40.2%) were females and 215 (59.7%) were males.

We also had the opportunity to address survival in several nonclassical MF subsets, which have been analyzed for survival in the literature (Table 2; ref. 10). Folliculotropic MF has been associated with reduced survival or progression compared with classic MF (10, 26). Hypopigmented or juvenile MF, more common in skin types III or IV, and poikiloderma have been suggested to have a more indolent clinical course (27). Clinical and histologic variants of MF included 45 folliculotropic MF (3.6%), 64 poikilodermatous MF (5.1%), 54 hypopigmented MF (4.3%), 45 MF with lymphomatoid papulosis (3.6%), and 109 MF with LCT in skin or nodes (8.7%).

The majority of patients with MF were diagnosed with skin stage T1 (<10% involvement; 41.2%) and T2 (>10% and <80% skin involvement; 32%). Using the EORTC staging proposal to classify early patients by T-stage at diagnosis (20), 382 of 520 T1 patients had patches (T1a), and 138 had patches and plaques (T1b). Among 403 T2 patients, 198 had patches (T2a), and 205 had patches and plaques (T2b). Eleven percent of all patients presented with skin tumors (T3). There were 184 patients (15.4%) with SS: erythroderma (T4) and B2 blood involvement. Seventy patients (5.6%) with criteria for SS had bone-marrow involvement at baseline. At initial presentation and staging, only 3 patients had extracutaneous disease in central nervous system, lung, or liver, excluding bone-marrow involvement.

Blood involvement by flow cytometry was assessed at baseline in all advanced patients and in the majority of early-stage patients. Among these 1,263 patients, 205 (16.2%) had some degree of blood involvement: 192 patients (15.2%) had B2 and 13 (1.0%) had B1. Ninety-four percent or 490 of 522 of stage IA (T1) patients had flow cytometry of blood conducted at baseline: 10 were B1 and 3 were B2. Thus, only 2.4% of early-stage IA patients had measurable SS cells by flow cytometry at baseline.

Serum LDH levels in 1,158 patients at baseline were normal in 890 or 77% of patients and were elevated (>618 IU/L) in 268 patients, including 92 early-stage patients and 176 advanced stage patients.

Standard treatment approach

Our treatment approach adopted in the mid-1980s was to identify and treat infections, to avoid use of immunosuppressive therapies for as long as possible, and to treat patients as conservatively as possible while trying for complete, durable remissions. In total, 578 of the patients in this analysis were treated on clinical trials including 39.6% (358/903) with early-stage MF and 61% (220/360) with advanced disease. The treatment algorithms used were similar to the recent National Cancer Center Network guidelines (28). Early-stage patients first received only skin-directed therapies. Biologic response modifiers or experimental agents were added if patients became refractory or progressed beyond IA (28).

As previously reported in 1996 (29) and updated in 2003 (30), beginning in 1987, all new patients with MF/SS ($n = 95$) with stage ≥IB (T2) received multimodality therapy on protocol: accutane and interferon × 4 months followed by total skin electron beam radiation and maintenance with interferon × 1 year, and topical nitrogen mustard maintenance for 2 years or if not in complete response, indefinitely until progression. Patients with advanced disease (>IIa), including nodal disease, also received multi-agent chemotherapy with cytoxan, methotrexate, etoposide, and dexamethasone × 6 cycles before their beam. The overall complete response rate for this study was 60% with a median OS of 145 and 36 months for early- versus late-stage patients, respectively (30). Patients who relapsed were treated by stage with either skin-directed therapy or experimental agents on clinical trials.

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

Table 2. Univariate analysis of ISCL/EORTC T-stage classification and effect of histologic and biochemical factors on OS, DSS, and PFS

	OS		DSS		PFS	
Classification	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
T classification						
T1a vs. T4	0.05 (0.03–0.09)	<0.0001	0.01 (0.01–0.075)	<0.0001	0.09 (0.05–0.14)	<0.0001
T1b vs. T4	0.17 (0.11–0.28)	0.21 (0.10–0.44)	0.43 (0.30–0.62)			
T2a vs. T4	0.08 (0.04–0.16)	0.06 (0.02–0.19)	0.14 (0.08–0.23)			
T2b vs. T4	0.33 (0.23–0.47)	0.31 (0.17–0.55)	0.57 (0.43–0.77)			
T3 vs. T4	0.68 (0.49–0.94)	1 (0.62–1.61)	0.75 (0.55–1.03)			
N classification						
N0 vs. N4	0.27 (0.17–0.45)	<0.0001	0.22 (0.10–0.46)	<0.0001	0.39 (0.24–0.62)	<0.0001
N1 vs. N4	0.37 (0.19–0.75)	0.32 (0.11–0.95)	0.55 (0.29–1.04)			
N2 vs. N4	0.98 (0.51–1.90)	1.11 (0.42–2.92)	0.99 (0.51–1.91)			
N3 vs. N4	0.92 (0.40–2.13)	1.09 (0.32–3.66)	0.88 (0.38–2.03)			
B classification						
B0 vs. B2	0.19 (0.15–0.25)	<0.0001	0.21 (0.14–0.32)	<0.0001	0.29 (0.23–0.37)	<0.0001
B1 vs. B2	0.11 (0.01–0.80)	0.31 (0.04–2.27)	0.51 (0.18–1.39)			
M classification						
M0 vs. M1	0.27 (0.19–0.38)	<0.0001	0.18 (0.11–0.29)	<0.0001	0.39 (0.28–0.54)	<0.0001
Sezary syndrome						
No vs. yes	0.2 (0.15–0.25)	<0.0001	0.21 (0.14–0.31)	<0.0001	0.39 (0.28–0.54)	<0.0001
Folliculotropic						
No vs. yes	1.19 (0.56–2.53)	0.64	1.6 (0.39–6.5)	0.5	1.07 (0.57–2.02)	0.81
Poikiloderma						
No vs. yes	2.83 (1.26–6.37)	0.01	6.7 (0.94–48.65)	0.06	1.63 (0.94–2.85)	0.08
Hypopigmented						
No vs. yes	1.56 (0.73–3.32)	0.24	2.06 (0.50–8.39)	0.3	1.51 (0.77–2.94)	0.22
MF with Lyp						
No vs. yes	5.58 (1.38–22.42)	0.02	4.23 (0.59–30.3)	0.15	2.76 (1.14–6.69)	0.02
LCT skin and node						
No vs. yes	0.13 (0.08–0.20)	<0.0001	0.06 (0.03–0.13)	<0.0001	0.33 (0.24–0.45)	<0.0001
Tumor distribution						
Localized vs. solitary	0.81 (0.36–1.78)	<0.0001	0.77 (0.23–2.52)	<0.0001	1.06 (0.52–2.15)	<0.0001
Regional vs. solitary	0.87 (0.25–2.94)	1.89 (0.51–7.02)	0.73 (0.21–2.44)			
Generalized vs. solitary	1.34 (0.74–2.41)	1.52 (0.65–3.56)	1.17 (0.66–2.08)			
LDH						
Normal vs. high	0.25 (0.19–0.32)	<0.0001	0.22 (0.15–0.34)	<0.0001	0.3 (0.24–0.37)	<0.0001
WBC						
Normal vs. high	0.35 (0.25–0.48)	<0.0001	0.27 (0.16–0.44)	<0.0001	0.42 (0.31–0.56)	<0.0001
Sex						
Female vs. male	0.84 (0.65–1.07)	0.16	0.91 (0.16–1.36)	0.67	0.87 (0.70–1.08)	0.22
β_2-Microglobulin						
<1.8 vs. >1.8	0.153 (0.08–0.26)	<0.0001	0.1 (0.03–0.28)	<0.0001	0.22 (0.14–0.34)	<0.0001
CD25 expression						
<20% vs. >20%	0.81 (0.58–1.15)	0.25	0.73 (0.44–1.19)	0.21	0.76 (0.56–1.03)	0.09
CD30 expression						
No vs. yes	0.92 (0.57–1.49)	0.76	0.98 (0.48–2.00)	0.97	1.03 (0.67–1.59)	0.87

After the completion of the combined modality therapy, new patients with SS were treated initially on multimodality therapy with extracorporeal photopheresis and biologic therapy as reported previously (21, 31) and on clinical trials if they progressed. In the 1990s, denileukin diftitox was studied in trials for early patients with <3 prior therapies ($n = 15$) and for advanced stage with >3 prior therapies ($n = 6$) as described (32, 33). After approval, it was used predominantly for late-stage patients with tumors as the first-line therapy. Beginning

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

in 1996, both early ($n = 10$) and late ($n = 30$) patients, who had failed at least one prior systemic therapy, were treated on oral bexarotene at 300 mg/m^2 (34, 35). After approval, bexarotene was used in combination with skin-directed therapies for refractory early patients and was also used as front-line systemic therapy. Among the 1,263 patients with MF in this analysis, 320 were treated with oral bexarotene, including 166 or 18.3% of 903 early-stagepatients and 42.7% or 154 of 360 of advanced-stage patients.

Advanced patients with tumors received radiation, single-agent monotherapy, or were enrolled on small phase II clinical trials. These included gemcitabine ($n = 25$; ref. 36), sapacitabine ($n = 11$), bexarotene plus interferon ($n = 7$), forodesine ($n = 47$), interleukin 12 ($n = 8$), CpG ($n = 12$), liposomal doxyrubicin ($n = 17$), humax CD4 monoclonal antibody ($n = 14$), histone deacetylase inhibitors vorinostat ($n = 39$; refs. 37, 38) and romidepsin ($n = 3$), panobinostat ($n = 12$), or praletrexate ($n = 15$; ref. 39). From 2001 to 2009, 19 advanced patients (5% of 360) received total body electron beam followed by allogeneic stem cell transplantation (40).

Overall and disease-free survival and deaths

Median OS for all patients with MF/SS was 24.44 years for the entire study period. The median OS for females was 32.04 years and was 20.70 years for males (Table 1). The median OS for patients whose age was less than 42 years was 35.8 years but for age more than 66 years, OS was only 7.6 years. The Kaplan–Meier plots of OS by National Cancer Institute (NCI) I–IV staging and by T-stages are shown in Fig. 1A and B.

Median DSS was not reached (Table 2). A total of 273 of 1,255 (21.8%) patients died, with 102 (37.4%) deaths attributed to MF/SS. Other related causes of death included sepsis ($n = 5$), pneumonia, renal failure, cardiopulmonary events, and secondary malignancies. Among 184 patients with SS, 106 (57.6%) died with a median OS of 4.98 years. Among patients with non-SS, 162 patients of 1,065 (15.2%) died, and the median survival was 29.28 years.

OS and DSS by skin T-stage

Although the median OS and DSS for T1 patients were not reached (Table 2, Fig. 2A), stage IA MF patients with only patches and no plaques (T1a) did significantly better than patients with both (T1b; Table 2). Likewise, although the OS and DSS were not reached for T2a patients (>10% patches only), OS was 16.9 years and DSS was 26.26 years for patients with T2b with >10% patch/plaque disease (Fig. 2A). Median OS for patients with tumors T3 was 5.96 years, similar to OS of 5.0 years for stage T4, erythrodermic patients (Fig. 1B). The OS rate by T-stage at 5, 10, and 20 years, respectively, was 95%, 89%, and 82% for T1; 87%, 78%, and 61% for T2; 57%, 46%, and 36% for T3; and 52%, 29%, and 12% for T4.

OS and DSS by node (N) classification

One hundred and thirty-eight patients (10.9%) had nodal disease (N1–N4) at diagnosis. Median OS for N0 was 26.26 years, and DSS was not reached for N0. Median

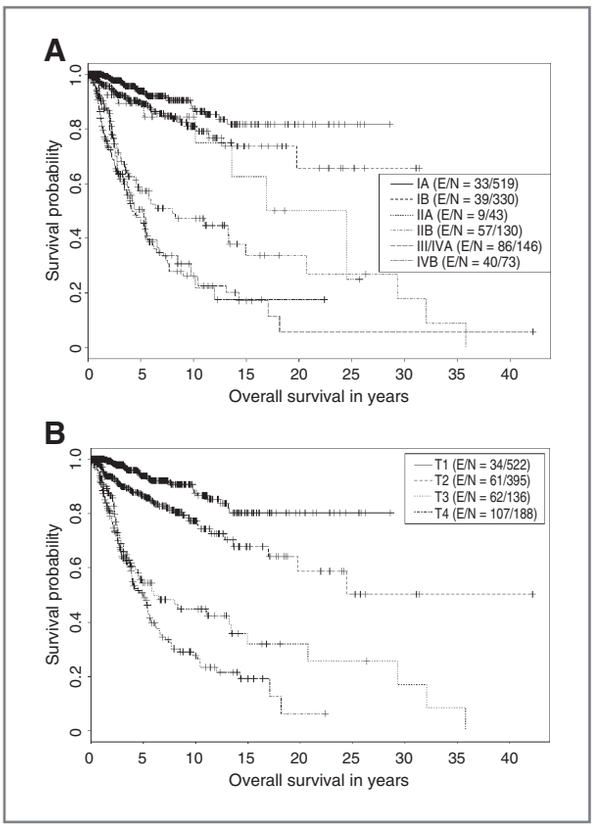

Figure 1. Survival outcomes by Kaplan–Meier. A, survival outcome by clinical TNM stage (IA, IB, IIA, IIB, III/IVA, and IVB). B, survival outcome according to T1–4 classification ISCL/EORTC (20).

OS for patients staged as N1–2 was 10.2 years, and as N3–4 was 4.47 years, compared with N0 (no nodal disease) OS of 26.26 years for N0 (Table 1). Worse outcomes were observed for N4 patients whose median OS was 2.85 years (Table 2). The DSS for N1–3 was 16.91 years and DSS for N4 (effacement) was 9.01 years.

OSS and DSS by peripheral blood (B) classification

Peripheral blood involvement by flow was present to some degree in 205 patients. Only 13 patients were classified as B1, whereas 192 had B2 involvement, and classified as SS (stage IVA1; Fig. 3). As expected, a significant difference in OS and DSS of patients was noted between those classified as B0 and B2 ($P < 0.0001$; Fig. 3). The sample size for B1 patients was too small for comparison. The OS for B2 was 4.64 years as compared with OS for patients with B0 of 29.28 years (Fig. 3). Of note, the DSS for B2 was 18.14 years, whereas for B0 was not reached.

OS and DSS by clinical stage (IA–IVB)

The majority of patients with MF (894 or 71.8%) presented at an early stage I–IIA MF with 360 (28.9%) presenting at advanced stages (≥IIB–IVB; Tables 1 and 2 and Figs. 1A and 2B). The predictive value of age was greater in stages I–III and less valuable in stage IVpatients. Not

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

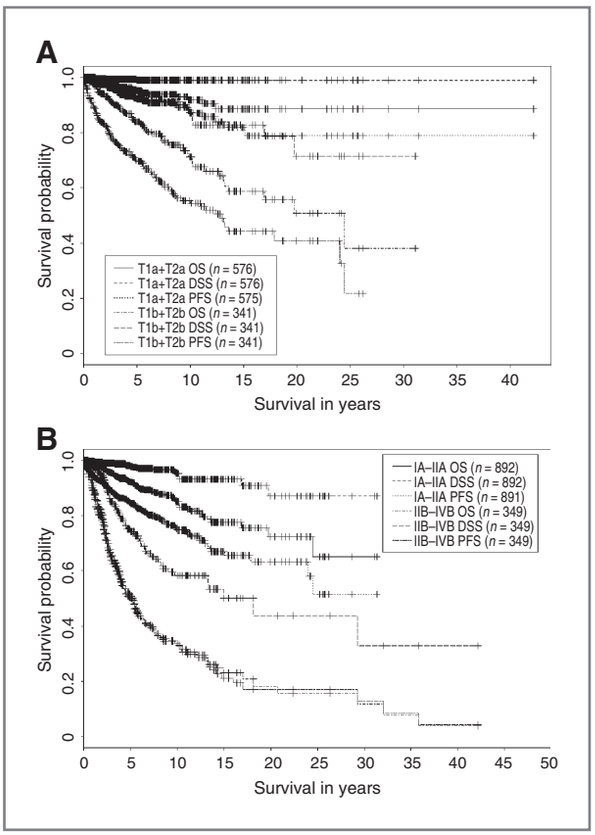

Figure 2. A, survival outcomes including OS, DFS, and PFS (A) comparing patch (T1a + T2a) with patch plaque (T1b + T2b); B, survival time by IA–IIA versus IIB–IVB TNM stages.

unexpectedly, patients who were staged as IIB–IV at diagnosis were more likely to have disease progression or die from MF than patients with early stage at diagnosis.

Progression-free survival

Analysis of PFS was defined as the first disease progression or MF-related death. The median PFS was 16.0 years for all patients. Figure 2B shows PFS by disease stage. The PFS for T1 was not reached, for T2 was 24 years, for T3 was 5.86 years, and for T4 was 5.00 years. By univariate analysis, earlier stage and younger age at diagnosis and Caucasian race were significantly associated with a favorable PFS. Disease progression was noted in 348 patients (27.6%), and there was an increased risk of disease progression with advancing age. The risk of progression of disease was significant for B2 as compared with B0–1 ($P < 0.0001$) because more patients with B2 disease died. Older patients (>55 years) and African Americans were more likely to have disease progression or die from MF than younger patients or Caucasian patients, respectively (41).

Prognostic factors

Advanced age at diagnosis was an important negative predictive factor in both univariate and multivariate analysis ($P < 0.01$). Advanced age (>66 years) at diagnosis was an important negative predictive factor in both univariate ($P < 0.0001$) and multivariate analysis ($P < 0.0001$). Levels of LDH, elevated WBC count, and β_2-microglobulin by univariate analysis were also significant ($P < 0.0001$; Table 2). LCT was associated with reduced OS/DSS and decreased PFS ($P < 0.0001$; Table 2). Expression of CD25 or CD30 in the skin biopsy had no significant effect on the survival (OS, DSS, and PFS). Generalized tumors compared with regional tumor(s) were associated with a significantly worse OS outcome than a solitary tumor ($P < 0.0001$; Table 2).

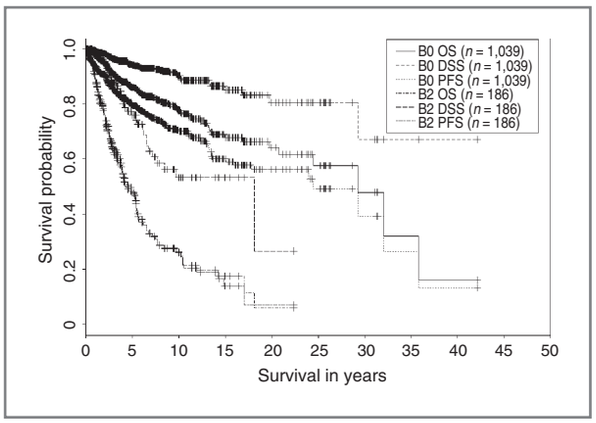

Figure 3. Survival outcomes OS, DFS, and PFS for blood stages B0, B1, and B2.

Among the relatively small numbers of patients with rarer MF variants (folliculotropic, poikiloderma, hypopigmented, and MF associated with lymphomatoid papulosis), only poikiloderma and MF with lymphomatoid papulosis had significantly better outcomes of OS/DSS and a reduced risk of disease progression compared with all patients with MF (Table 2).

Discussion

This is the largest, to date, single institution, U.S. study to report survival and risk factors for progression from MF and SS. Our cohort consists of 1,263 patients with MF/SS with a mean age of 55.53 years prospectively followed and treated by a single clinician for 27 years. Kim and colleagues previously reported inferior survival in stage IB (>10% patch or plaques) as compared with IA patients (<10% patches or plaques) in a cohort of 525 patients. Because of her observation, new T1a/b and T2a/b substages were incorporated into the ISCL/EORTC new staging revisions to be examined in future CTCLs cohorts (4, 5, 10, 20). We are the first U.S. center to validate the ISCL/EORTC revised T1 and T2 staging for patch versus patch/plaque subsets (T1a/b and T2a/b). Our study also confirms the difference in T1 and T2 subsets reported recently by Agar and colleagues in a large British cohort of 1,502 patients with median age of 54 years, followed up for 29 years in the same time period (1980–2009; ref. 10). Both studies found that inferior survival was associated with the presence of plaques (T1b/T2b) in patients with stage IA and IB. Our study also further validates prognostic markers including advanced

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

age, LDH, and β_2-microglobulin levels, white count, and presence of LCT in univariate analysis.

An unexpected finding in our cohort was the near equal ratio of females 1.1:1 to males because a male–female predominance ratio of 1.72 was reported from the SEER database analysis (2). The overall male to female incidence in our cohort was almost equal among the early-stage patients (48.9% female, 51% male). Others reported that the incidence among males exceeds females but did examine stage (3, 7, 10). In our study, males represented a higher proportion of advanced stages (59.7% males and 40.3%, females). But in early-stage (IA–IIA) MF patients ($n = 903$), representing 71.5% of the cohort, 447 (49.5%) were females and 456 (50.5%) were males. The overall proportion of early-stage patients (71.5%) was identical to 71% reported by Agar and colleagues (10) and was also similar to 66.8% early patients in the Stanford cohort (9). In our study, the percentage of males (59.7%; 215) outnumbered females (40.2%; 145) in the 360 patients with advanced stages at diagnosis, but the ratio was no different in early disease.

Another difference is that OS among female patients was 32.04 years compared with only 20.7 years in male MF patients, but the *P*-value was not significant. A subgroup of young African American females in our cohort may have inferior survival and increased risk of progression (41). In the recent British study, median OS was also superior in females (24.1 years) as compared with males (13.4 years; $P \leq 0.001$; ref. 10). In the 525-patient 1993 Stanford cohort, an OS of 13.5 years was reported for females versus 10 years for males (9). Thus, inferior OS in males versus females has now been reported in 3 studies including our own. The reason for the higher incidence of males with MF and their increased representation at higher stages is unknown.

OS for the early T1 patients was not reached in our cohort as reported in the 2003 Stanford cohort of Kim and colleagues (9). OS for T1 was 35.5 years in the British study with 29 years of follow-up similar to 24.44 years with 27-year follow-up in our study (10). Favorable OS is likely influenced by the high percentage (71%) of early-stage MFpatients within all the cohorts. In Agar and colleagues (10), median survival and OS/DSS decreased as skin stage (T1–4) progressed, and disease progression increased with advancing age. Kim and colleagues also reported that the risk of disease progression worsened with advanced T classification finding greater risk in patients with T2 compared with T1 ($P < 0.001$) and in T3 or T4 compared with T2 ($P < 0.001$; ref. 9). Tumor–node–metastasis, system for staging cancer (TNM) stage beyond IA was associated with inferior survival, whereas IA patients' survival was no different than age matched controls (4, 9).

Among our T2 patients, improved OS and DFS were noted for T2a (>10% body with patches only) compared with T2b (>10% plaques with patches; OS - $P < 0.0001$; DSS $P = 0.003$). In the retrospective cohort analysis of T2 patients at Stanford over 35.5 years, disease progression occurred in 20% of T2 patients, with patches and plaques and was significantly worse than sex-matched controls (5). These studies suggest that patients with plaques need aggressive topical and systemic therapy compared with patients with patches who may be managed by skin-directed therapy alone.

The influence of blood involvement on survival and PFS is a moving target as more sensitive flow cytometry studies and markers are replacing manual cell counts at most CTCL centers (23). The presence of a T-cell clone in peripheral blood was found to be an independent prognostic marker for patients with MF (15). The revised EORTC/ISCL staging system proposed grading blood involvement as B0 (<5% or absence of blood), B1 (aleukemic >500 and <1,000 cells/μL), or B2 (leukemic >1,000 cells/μL; ref. 20), replacing the former B0 or B1 criteria. Erythroderma (T4) with B2 was classified as SS. Erythrodermic CTCLs with B2 blood involvement defining SS has been associated with poor outcome and OS. The study done by Kim and colleagues (9) reported an OS of only 2.5 years, whereas the study done by Agar and colleagues study reported a 3.1 year OS in patients with SS (10).

Our study has shown superior survival for patients with blood involvement in this American cohort. We prospectively collected flow cytometry data on almost all patients at baseline regardless of stage. Only 12 of 490 IA patients (2.4%) had abnormal baseline flow cytometry: 10 had B1 and 3 had B2 blood involvement. None of the B1 patients had nodal involvement, and there was no significant difference in the survival between B0 and B1 in early-stage-patients. The British group previously reported that H4 or >10,000 SS cells/μL was associated with poor OS of 2.5 years (42). Our previous retrospective analysis of 124 erythrodermic (T4) patients reported by Vidulich and colleagues (16), reported that OS was 5.1 years in erythrodermic patients regardless of degree of blood involvement, 7.6 years for B0–B1 (H0-2), 5.4 years for H3 (B2 >1,000–<10,000), and only 2.4 years for H4 blood involvement (>10,000 SS cells/μL; ref. 16). Five- and 10-year survival estimates were 51% and 29% for all patients with erythrodermic CTCL. In the current analysis, OS for patients with B2 was 4.64 years compared with OS of 29.28 years with no blood involvement (Fig. 3). DSS for B2 was 18.14 years and for B0 was not reached. Our recent analysis suggests that B2 involvement confers a significant difference in the OS and DSS between B0 and B2 ($P < 0.001$) but that "H4" or "B3" (>10,000 SS cells/μL) has the worst prognosis and could be used to stage blood.

The Stanford report included 35 patients with SS whose OS was 3 years for B1 (now B2 > 1,000 SS cells/μL). Many of the patients with SS also had nodal involvement, which may have influenced survival in their patients (9). The major cause of death in patients with erythroderma and SS is line sepsis, which is often from *Staphylococcus aureus*. *Staphylococcus* was prospectively cultured from 60% of patients with SS from our center and was aggressively treated and prevented with antibiotics and skin care (43).

Others and we identified LDH and B-2 macroglobulin as independent prognostic markers (13, 16). Elevated serum

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

LDH was an independent predictor of poor survival and increased progression risk in univariate and multivariate analysis (10, 16). Elevated β_2-microglobulin levels were also associated with a reduction in median survival. Our patients with β_2-microglobulin more than 1.8 mg/L had reduction in median survival and progression of disease but this may reflect an age effect, as older age was associated with poor prognosis as well as rising β_2-microglobulin levels (42). A Sézary cell count of 10,000 μL or more was another significant prognostic factor for survival and progression risk in univariate analysis as we have previously suggested (16).

In the study done by Agar and colleagues (10), folliculotropic MF, in 189 patients, showed increased risk of disease progression in univariate analysis. In the multivariate model, folliculotropism became an independent significant factor for survival and progression outcomes (10). Our study did not show an increased risk of progression or examine treatment differences. Our study had a smaller sample size with folliculotropic MF representing only 3.6% of all our patients compared with 12.6% in the British cohort (10).

LCT has been associated with progression and poor outcome, especially when it occurs within 2 years of diagnosis (13, 17). In a small study of 115 patients with MF or SS reported from MDACC, the incidence of LCT was 26% with a cumulative probability of 39% over 12 years (17). In our larger cohort of 1,263 patients, only 8.7% patients had biopsy-proven LCT in skin. This is comparable with the incidence of 5% previously reported by Agar and colleagues (10). LCT was associated with increased risk of disease progression and decreased median OS and DSS in both univariate and multivariate analysis ($P = 0.0001$; Table 2). Of interest, T-cell biomarkers including CD25 (the α chain of the T-cell receptor) and CD30 (a TNF-like receptor), often associated with LCT, were not significant for any of the 3 survival outcomes (OS, DSS, and PFS).

Like the Agar and colleagues study (10), our purpose was to validate the ISCL/EORTC revised staging for MF/SS (20), and to confirm outcome in early versus late stages. Outcome analysis of the 2 U.S. and British cohorts may allow validation of a Cutaneous Lymphoma International Prognostic Index. Confirmation of prognostic variables should allow identification of patients to select for more aggressive therapy based on risk category. Improved outcome reflected in OS, PFS, and DFS at all stages in our cohort may result from earlier diagnosis, access to new therapies, and early treatment of coexisting infections.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Talpur, S. Daulat, M. Duvic
Development of methodology: R. Talpur, L. Singh, S. Daulat, M. Duvic
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Talpur, L. Singh, S. Daulat, M. Duvic
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Talpur, L. Singh, S. Daulat, P. Liu, W. Wei, M. Duvic
Writing, review, and/or revision of the manuscript: R. Talpur, L. Singh, S. Daulat, P. Liu, W. Wei, M. Duvic
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Daulat, S. Seyfer, T. Trynosky

Grant Support

This research was supported by the NCI MDACC Core Grant CA16672-22, NCI (R21-CA74117), NIAMS K24 CA 86815, the Sherry L Anderson fund for CTCL Research, and by the CTCL patient education and research fund.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 21, 2012; revised July 11, 2012; accepted July 24, 2012; published OnlineFirst July 31, 2012.

References

1. Campbell JJ, Clark RA, Watanabe R, Kupper TS. Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct behavior. Blood 2010;116:767–71.
2. Barton PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population based study of 3884 cases. Blood 2009;113:5064–73.
3. Criscione VD, Weinstock MA. Incidence of cutaneous T cell lymphoma in United States, 1973–2002. Arch Dermatol 2007;143:854–9.
4. Zackheim HS, Amin S, Kashani-Sabet M, McMillan A. Prognosis in cutaneous T-cell lymphoma by skin stage. J Am Acad Dermatol 1999;40:418–25.
5. Kim YH, Chow S, Varghese A, Hoppe RT. Clinical characteristics and long-term outcome of patients with generalized patch and/or plaque (T2) mycosis fungoides. Arch Dermatol 1999;135:26–32.
6. Sausville EA, Eddy JL, Makuch RW, Fischmann AB, Schechter GP, Matthews M, et al. Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome: definition of three distinctive prognostic groups. Ann Intern Med 1988;109:372–82.
7. Weinstock MA, Reynes JF. The changing survival of patients with mycosis fungoides: a population-based assessment of trends in the United States. Cancer 1999;85:208–12.
8. van Doorn R, Van Haselen CW, van Voorst Vader PC, Geerts ML, Heule F, de Rie M, et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol 2000;136:504–10.
9. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857–66.
10. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010;28:4730–9.
11. Marti RM, Estrach T, Reverter JC, Mascaro JM. Prognostic clinicopathologic factors in cutaneous T-cell lymphoma. Arch Dermatol 1991;127:1511–6.
12. Vonderheid EC, Diamond LW, van Vloten WA, Scheffer E, Meijer CJ, Cashell AW, et al. Lymph node classification systems in cutaneous T-cell lymphoma. Evidence for the utility of the working formulation of non-Hodgkin's lymphomas for clinical usage. Cancer 1994;73:207–18.
13. Diamandidou E, Colome M, Fayad L, Duvic M, Kurzrock R. Prognostic factor analysis in mycosis fungoides/Sézary syndrome. J Am Acad Dermatol 1999;40:914–24.

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

14. Bernengo MG, Quaglino P, Novelli M, Cappello N, Doveil GC, Lisa F, et al. Prognostic factors in Sézary syndrome: a multivariate analysis of clinical, haematological and immunological features. Ann Oncol 1998;9:857–63.
15. Fraser-Andrews EA, Woolford AJ, Russell-Jones R, Seed PT, Whittaker SJ. Detection of a peripheral blood T cell clone is an independent prognostic marker in mycosis fungoides. J Invest Dermatol 2000;114: 117–21.
16. Vidulich KA, Talpur R, Bassett RL, Duvic M. Overall survival in erythrodermic cutaneous T-cell lymphoma: an analysis of prognostic factors in a cohort of patients with erythrodermic cutaneous T-cell lymphoma. Int J Dermatol 2000;48:243–52.
17. Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sézary syndrome. Blood 1998; 92:1150–9.
18. Vergier B, de Muret A, Beylot-Barry M, Vaillant L, Ekouevi D, Chene G, et al. Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. French study group of cutaneous lymphomas. Blood 2000;95:2212–8.
19. Wasik MA, Vonderheid EC, Bigler RD, Marti R, Lessin SR, Polansky M, et al. Increased serum concentration of the soluble interleukin-2 receptor in cutaneous T-cell lymphoma: clinical and prognostic implications. Arch Dermatol 1996;132:42–7.
20. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713–22.
21. Raphael BA, Shin DB, Suchin KR,, Morrissey KA, Vittorio CC, Kim EJ, et al. High clinical response rate of Sézary syndrome to immunomodulatory therapies: prognostic markers of response. Arch Dermatol 2011;147:1410–5.
22. Vega F, Medeiros LJ, Jones D, Abruzzo LV, Lai R, Manning J, et al. A novel four-color PCR assay to assess T-cell receptor gamma gene rearrangements in lymphoproliferative lesions. Am J Clin Pathol 2001; 116:17–24.
23. Jones D, Dang NH, Duvic M,, Washington LT, Huh YO. Absence of CD26 expression is a useful marker for diagnosis of T-cell lymphoma in peripheral blood. Am J Clin Pathol 2001;115:885–92.
24. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
25. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
26. Lehman JS, Norris RC, Weed BR. Folliculotropic mycosis fungoides-single center study and systematic review. Arch Dermatol 2010;146: 607–13.
27. Wain EM, Orchard GE, Whittaker SJ, Spittle MSc MF, Russell-Jones R. Outcome in 34 patients with juvenile-onset mycosis fungoides. A clinical, immunophenotypic, and molecular study. Cancer 2003;98: 2282–90.
28. Zelenetz AD, Abramson JS, Advani RH, Andreadis CB, Byrd JC, Czuczman MS, et al. NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas. J Natl Compr Cancer Netw 2010;8: 288–334.
29. Duvic M, Lemak NA, Redman JR,, Eifel PJ, Tucker SL, Cabanillas FF, et al. Combined modality therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 1996;34:1022–9.
30. Duvic M, Apisarnthanarax N, Cohen DS, Smith TL, Ha CS, Kurzrock R. Analysis of long term outcomes of combined modality therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 2003;49: 35–49.
31. Duvic M, Chiao N, Talpur R. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma. J Cutan Med Surg 2003; 7:3–7.
32. Olsen E, Duvic M, Frankel A, Kim Y, Martin A, Vonderheid E, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol 2001;19: 376–88.
33. Prince HM, Duvic M, Martin A, Sterry W, Assaf C, Sun Y, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol 2010;28:1870–7.
34. Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. J Clin Oncol 2001;19:2456–71.
35. Duvic M, Martin AG, Kim Y, Olsen E, Wood GS, Crowley CA, et al. Phase 2 and 3 clinical trial of oral bexarotene (targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581–93.
36. Duvic M, Talpur R, Wen S,, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma Leuk 2006;7: 51–8.
37. Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007; 109:31–9.
38. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109–15.
39. Horwitz SM, Kim YH, Foss F, Zain JM, Myskowski PL, Lechowicz MJ, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). Blood 2012;119:4115–22.
40. Duvic M, Donato M, Dabaja B, Richmond H, Singh L, Wei W, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol 2010;28:2365–72
41. Sun G, Berthelot C, Li Y, Glass DA II, George D, Pandya A, et al. Poor prognosis in non-Caucasian patients with early-onset mycosis fungoides. J Am Acad Dermatol 2009;60:231–5.
42. Scarisbrick JJ, Whittaker S, Evans AV, Fraser-Andrews EA, Child FJ, Dean A, et al. Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. Blood 2001;97:624–30.
43. Talpur R, Bassett R, Duvic M. Prevalence and treatment of *Staphylococcus aureus* colonization in patients with mycosis fungoides and Sézary syndrome. Br J Dermatol 2008;159:105–12.

Published OnlineFirst July 31, 2012; DOI: 10.1158/1078-0432.CCR-12-0604

AACR American Association for Cancer Research

Clinical Cancer Research

Long-term Outcomes of 1,263 Patients with Mycosis Fungoides and Sézary Syndrome from 1982 to 2009

Rakhshandra Talpur, Lotika Singh, Seema Daulat, et al.

Clin Cancer Res 2012;18:5051-5060. Published OnlineFirst July 31, 2012.