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

Rakhshandra Talpur¹, Lotika Singh¹, Seema Daulat¹, Ping Liu², Sarah Seyfer¹, Tanya Trynosky¹, Wei Wei², and Madeleine Duvic¹

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.

**Introduction**

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin 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), β₂-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
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 hematologic 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 β₂-microglobulin levels (n = 834) at baseline. When indicated by stage >IA, patients underwent additional staging
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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Long-term outcome of 525 patients (Kim and colleagues; 9)</th>
<th>Validation of ISCL/EORTC. 1,502 patients (Agar and colleagues; 10)</th>
<th>MDACC study of 1,263 MF/SS patients</th>
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<tbody>
<tr>
<td>Mycosis fungoides (n)</td>
<td>490</td>
<td>1,398</td>
<td>1,062</td>
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<tr>
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<td>104</td>
<td>186</td>
</tr>
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<td>933</td>
<td>663</td>
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<td>20.7 y</td>
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<td>569</td>
<td>585</td>
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<tr>
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<td>13.5 y</td>
<td>24.1 y</td>
<td>32.0 y</td>
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<td>159</td>
<td>443</td>
<td>521</td>
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<td>Median OS</td>
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<td>Not reached</td>
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<td>T2 (n)</td>
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<td>395</td>
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<td>21.5 y</td>
<td>26.26 y</td>
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<td>Median OS</td>
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<td>4.1 y</td>
<td>5.96 y</td>
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<td>T4 (n)</td>
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<td>Median OS</td>
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<td>3.9 y</td>
<td>5.00 y</td>
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<td>Median OS</td>
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<td>Median OS</td>
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<td>Hypopigmented MF (n)</td>
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<td>54</td>
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<td>32.04 y</td>
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<td>Lyp and MF (n)</td>
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<td>Median OS</td>
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<td>Not reached</td>
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<td>1042</td>
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<td>24.5 y</td>
<td>29.28 y</td>
</tr>
<tr>
<td>B1 (n)</td>
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<td>71</td>
<td>13</td>
</tr>
<tr>
<td>Median OS</td>
<td>3 y</td>
<td>3.2 y</td>
<td>Not reached</td>
</tr>
<tr>
<td>B2 (n)</td>
<td>0</td>
<td>104</td>
<td>186</td>
</tr>
<tr>
<td>Median OS</td>
<td>3.1 y</td>
<td></td>
<td>4.64 y</td>
</tr>
<tr>
<td>N0 (n)</td>
<td>345</td>
<td>1,220</td>
<td>1,112</td>
</tr>
<tr>
<td>Median OS</td>
<td>17.4 y</td>
<td>22.8 y</td>
<td>26.26 y</td>
</tr>
<tr>
<td>N1 (n)</td>
<td>147</td>
<td>87</td>
<td>55</td>
</tr>
<tr>
<td>Median OS</td>
<td>6.5 y</td>
<td>5.2 y</td>
<td>16.91 y</td>
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<td>N2 (n)</td>
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<td>28</td>
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<tr>
<td>Median OS</td>
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<td>5.43 y</td>
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<tr>
<td>N3 (n)</td>
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<td>40</td>
<td>18</td>
</tr>
<tr>
<td>Median OS</td>
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<td>2 y</td>
<td>6.13 y</td>
</tr>
<tr>
<td>N4 (n)</td>
<td></td>
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</tr>
<tr>
<td>Median OS</td>
<td></td>
<td></td>
<td>2.85 y</td>
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<tr>
<td>Extracutaneous (n)</td>
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<td>13</td>
<td>70</td>
</tr>
<tr>
<td>Median OS</td>
<td>1.1 y</td>
<td></td>
<td>4.42 y</td>
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</tbody>
</table>
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 poikilodermia 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 immuno-suppressive 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 (>IA), 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.
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

<table>
<thead>
<tr>
<th>Classification</th>
<th>OS HR (95% CI) P</th>
<th>DSS HR (95% CI) P</th>
<th>PFS HR (95% CI) P</th>
</tr>
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<tbody>
<tr>
<td><strong>T classification</strong></td>
<td></td>
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<tr>
<td>T1a vs. T4</td>
<td>0.05 (0.03–0.09)</td>
<td>&lt;0.0001</td>
<td>0.01 (0.01–0.075)</td>
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<td>T1b vs. T4</td>
<td>0.17 (0.11–0.28)</td>
<td>0.2 (0.10–0.44)</td>
<td>0.43 (0.30–0.62)</td>
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<td>T2a vs. T4</td>
<td>0.08 (0.04–0.16)</td>
<td>0.06 (0.02–0.19)</td>
<td>0.14 (0.08–0.23)</td>
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<tr>
<td>T2b vs. T4</td>
<td>0.33 (0.23–0.47)</td>
<td>0.31 (0.17–0.55)</td>
<td>0.57 (0.43–0.77)</td>
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<tr>
<td>T3 vs. T4</td>
<td>0.68 (0.49–0.94)</td>
<td>1 (0.62–1.61)</td>
<td>0.75 (0.55–1.03)</td>
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<tr>
<td><strong>N classification</strong></td>
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<tr>
<td>NO vs. N4</td>
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<td>0.22 (0.10–0.46)</td>
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<tr>
<td>N1 vs. N4</td>
<td>0.37 (0.19–0.75)</td>
<td>0.32 (0.11–0.95)</td>
<td>0.55 (0.29–1.04)</td>
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<td>N2 vs. N4</td>
<td>0.98 (0.51–1.90)</td>
<td>1.11 (0.42–2.92)</td>
<td>0.99 (0.51–1.91)</td>
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<tr>
<td>N3 vs. N4</td>
<td>0.92 (0.40–2.13)</td>
<td>1.09 (0.32–3.66)</td>
<td>0.88 (0.38–2.03)</td>
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<td><strong>B classification</strong></td>
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<tr>
<td>B1 vs. B2</td>
<td>0.11 (0.01–0.80)</td>
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<td>0.51 (0.18–1.39)</td>
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<td>0.18 (0.11–0.29)</td>
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<td><strong>Sezary syndrome</strong></td>
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<td>&lt;0.0001</td>
<td>0.21 (0.14–0.31)</td>
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<tr>
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<td>1.6 (0.39–6.5)</td>
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<td>4.23 (0.59–30.3)</td>
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<td>0.77 (0.23–2.52)</td>
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<td>Normal vs. high</td>
<td>0.25 (0.19–0.32)</td>
<td>&lt;0.0001</td>
<td>0.22 (0.15–0.34)</td>
</tr>
<tr>
<td><strong>WBC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vs. high</td>
<td>0.35 (0.25–0.48)</td>
<td>&lt;0.0001</td>
<td>0.27 (0.16–0.44)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female vs. male</td>
<td>0.84 (0.65–1.07)</td>
<td>0.16</td>
<td>0.91 (0.16–1.36)</td>
</tr>
<tr>
<td>β2-Microglobulin &lt;1.8 vs. &gt;1.8</td>
<td>0.153 (0.08–0.26)</td>
<td>&lt;0.0001</td>
<td>0.1 (0.03–0.28)</td>
</tr>
<tr>
<td>CD25 expression</td>
<td>0.81 (0.58–1.15)</td>
<td>0.25</td>
<td>0.73 (0.44–1.19)</td>
</tr>
<tr>
<td>No vs. yes</td>
<td>0.92 (0.57–1.49)</td>
<td>0.76</td>
<td>0.98 (0.48–2.00)</td>
</tr>
</tbody>
</table>

HR (hazard ratio), CI (confidence interval), OS (overall survival), DSS (disease-specific survival), PFS (progression-free survival).
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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/m² (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-stage patients 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 doxycycline (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 pralatrexate (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 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 in Fig. 1A and B.

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 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 OS for patients staged as N1–2 was 10.2 years, and as N3–4 was 4.64 years as compared with OS for patients with B0 of 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.

OS 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 B1–3 was 16.91 years and DSS for N4 (effacement) was 9.01 years.

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 (≥IIIB–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 IV patients. Not
Prognostic factors

Advanced age at diagnosis was an important negative predictor factor in both univariate and multivariate analysis ($P < 0.01$). Advanced age (>66 years) at diagnosis was an important negative predictor factor in both univariate ($P < 0.0001$) and multivariate analysis ($P < 0.0001$). Levels of LDH, elevated WBC count, and $\beta_2$-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).

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
age, LDH, and β2-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 1:2 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 < 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 27-year follow-up in our study (10). Favorable OS is likely influenced by the high percentage (71%) of early-stage MF patients 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 for B0–B1 and 1,000 SS cells/μL was associated with poor OS of 2.5 years (42). The Stanford report included 35 patients with SS whose OS was 3 years for B1 (now B2) and 3 years for B2 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
LDH was an independent predictor of poor survival and increased progression risk in univariate and multivariate analysis (10, 16). Elevated β2-microglobulin levels were also associated with a reduction in median survival. Our patients with β2-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 β2-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 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.

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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. Snyder, T. Trynosky

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References


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