Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation

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Although mycosis fungoides (MF) is typically an indolent disease, patients with advanced-stage disease (stages IIB-IVB), including Sézary syndrome (SS), often have a poor outcome. A 31-year, retrospective analysis of our cutaneous lymphoma database, of 297 patients with MF and SS, was undertaken to study long-term outcomes and identify clinical predictors of outcome in patients with advanced-stage disease (ASD, n = 92) and large cell transformation (LCT, n = 22). Two-thirds of patients with ASD presented with de novo ASD. The median overall survival (OS) for ASD was 5 years with a 10-year predicted OS of 32%. Age at initial diagnosis (P = .01), tumor stage (P = .01), and clinical stage (P = .001) were found to be significant predictors of outcome. Patients who presented with de novo ASD demonstrated better outcomes that were not statistically significant than those with a prior diagnosis of early-stage MF (P = .25). Transformation developed in 22 of the 297 MF/SS patients (7.4%), with a transformation rate of only 1.4% in patients with early-stage disease, compared with stage IIB (27%) and stage IV (56%-67%) disease. The median OS from diagnosis of LCT was 2 years. We confirm that the incidence of LCT is strongly dependent on tumor stage at diagnosis, and we demonstrate a much lower overall risk of LCT than previously reported. (Blood. 2008;112:3082-3087)

Introduction

Cutaneous T-cell lymphomas (CTCLs) are a clinically and histologically diverse group of T lymphocyte malignancies that manifest in the skin. Mycosis fungoides (MF) is the most common subtype of CTCL, and typically runs an indolent course. Sézary syndrome (SS) is a rare subtype of CTCL that is traditionally defined as the triad of erythroderma, lymphadenopathy, and the presence of circulating monoclonal T lymphocytes with distinctive cerebriform nuclei (Sézary cells (SCs)).

According to the original Mycosis Fungoides Cooperative Group (MFCG) staging system,2 advanced-stage MF/SS includes clinical stages IIB, III, IVA, and IVB (Table 1). Patients with advanced-stage MF/SS present with one or more of the following clinical features: tumor lesions (stage IIB), erythroderma (stage III, if in the absence of nodal or visceral disease), histologic lymph node involvement (stage IVA, irrespective of T stage), and visceral disease (stage IVB, irrespective of T and N stages). Because the MFCG staging system does not take blood involvement into account when determining overall clinical stage, patients with SS are generally staged as stage III, unless lymph node (stage IVA) or visceral disease (stage IVB) is present. Previous studies have demonstrated that the prognosis of advanced-stage disease (ASD) is generally poor1-4; median overall survival (OS) in patients with tumor, erythrodermic, and extracutaneous disease have been reported to be 40, 48, and 13 months, respectively.

The occurrence of large cell transformation (LCT) in MF/SS, although rare, has been well described.5-10 LCT is pathologically characterized by the morphologic change of small- to medium-sized cerebriform cells to a large cell variant,11 accompanied by clinically aggressive disease. Large cells are lymphocytes that are at least 4 times greater in size than a small lymphocyte. The diagnosis of LCT is made in the presence of a consistent patient history, MF histology on skin biopsy, and large cells exceeding 25% of the total lymphoid infiltrate or microscopic tumor nodules of large cells in a skin lesion.5-8 Molecular analysis has shown that the transformed clonal population is derived from the original T-cell clone present in MF.12,13 Large cells may or may not express the CD30 antigen.

The incidence of LCT has previously been reported to be between 11% and 23% where the diagnostic criterion is the presence of a large cell population on biopsy composing greater than 25% of the total lymphoid infiltrate or microscopic tumor nodules of large cells in a skin lesion.5-8 Transformation occurs more commonly in advanced-stage disease than early-stage disease (ESD)9 and is especially common in tumor lesions (LCT in 55% of patients with tumor-stage disease in one study).10 The prognosis of LCT is significantly worse than in classic MF. The median survival from initial diagnosis of MF/SS has been reported as 37 months for patients with LCT, compared with 163 months in the group with no transformation.7 The median survival after the diagnosis of transformation has been reported as between 12 months2 and 22 months.8 The following characteristics have been associated with poorer survival5-7,8: (1) LCT in an extracutaneous site; (2) transformation early in the disease course (< 2 years from the diagnosis of LCT vs > 2 years); (3) transformation in ASD; and (4) elevated β2-microglobulin and lactate dehydrogenase (LDH). Sex, age, percentage of large cells, and CD30 expression did not appear to have prognostic significance.

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As a multidisciplinary center for cutaneous lymphoma, the Department of Dermatology, St Vincent’s Hospital Melbourne and the Department of Hematology, Peter MacCallum Cancer Center have maintained a cutaneous lymphoma database for more than the past 3 decades. The aims of this study were to evaluate the long-term survival of: (1) patients with advanced-stage MF and SS and (2) patients with LCT.

Methods
Institutional Review Board approval for this study was obtained from the Peter MacCallum Cancer Center, East Melbourne, Australia.

Study design
Analysis of the cutaneous lymphoma database, containing 358 patients with CTCL presenting more than a 31-year period, was undertaken. A retrospective analysis was performed on 92 patients with advanced-stage MF/SS (including 3 patients with an early stage of disease and LCT), and 22 patients with LCT, from a population of 297 patients with MF or SS. Patients were managed at the St Vincent’s/Peter MacCallum Cutaneous Lymphoma Clinic. The database is updated on a monthly basis and the close-out date for the analysis was October 31, 2007.

Clinical evaluation and definitions
All patients had a biopsy-proven diagnosis of MF. For staging purposes, patients underwent a physical examination, a full blood examination with analysis of the blood film for SCs, LDH, and β2 microglobulin. Patients with clinically significant lymphadenopathy (> 3-4 cm on palpation or computed tomography (CT)), and in whom infection was not considered a risk, underwent core or excisional lymph node biopsy for evaluation. Visceral involvement was evaluated using CT. Repeat skin biopsies were performed in patients who demonstrated clinically progressive disease.

Leukemic involvement in erythrodermic patients (hence, SS) was diagnosed if an abnormal T-cell population was identified using 2 or more of the following methods: (1) T-cell receptor gene rearrangement studies by polymerase chain reaction, demonstrating peripheral blood clonality; (2) immunophenotyping studies, demonstrating a CD4/CD8 ratio of greater than 10; and (3) SCs that comprised greater than 5% of the total lymphocyte count on blood film. Flow cytometry was used for immunophenotypic analysis of the circulating malignant clone. Patients were staged using the MFCG staging system (Table 1). Patients were staged as stage IVB if visceral disease (including splenomegaly and excluding bone marrow disease) was present, consistent with the original MFCG staging system and the new International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer staging system.

In accordance with previously defined criteria, LCT was diagnosed if at least one skin biopsy showed a population of large cells that were greater than 4 times the size of small lymphocytes exceeding 25% of the total lymphoid infiltrate. In all cases, immunophenotypic studies by immunohistochemistry were performed to determine whether large cells expressed the CD30 antigen. Bone marrow and lymph node biopsies were performed at the clinicians’ discretion to assess for extracutaneous large cell involvement.

Disease progression was defined to include stage progression (disease progression to a higher clinical stage), transformation to large cell lymphoma, or development of leukemic involvement in patients with erythrodermic disease.

Data analysis
Statistical analysis was performed using GraphPad Prism Software (version 3.02; San Diego, CA) statistical software. Survival data were analyzed using the Kaplan-Meier method. Survival curves were compared using the log-rank test.

Table 1. Original Mycosis Fungoides Cooperative Group staging system for cutaneous T-cell lymphoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor (T)</th>
<th>Lymph node (N)</th>
<th>Metastasis (M)</th>
<th>Blood (B)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>T1: patches/plaques over &lt; 10% of skin surface</td>
<td>N0: no palpable lymphadenopathy or histologic involvement</td>
<td>M0: no visceral involvement</td>
<td>B0: &lt; 5% SC; B1: &gt; 5% SC and no more than one clone in blood; SC</td>
</tr>
<tr>
<td>IB</td>
<td>T2: patches/plaques over &gt; 10% of skin surface</td>
<td>N0</td>
<td>M0</td>
<td>of the following: T-cell clone in blood; SC</td>
</tr>
<tr>
<td>IIA</td>
<td>T1 or T2</td>
<td>N1: palpable lymphadenopathy, no histologic involvement</td>
<td>M0</td>
<td>count &gt; 1 × 10^8/L; CD4:CD8 ≥ 10;</td>
</tr>
<tr>
<td>Advanced stages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>T3: tumors</td>
<td>N0 or N1</td>
<td>M0</td>
<td>clone in blood and either</td>
</tr>
<tr>
<td>IVA</td>
<td>T4: erythroderma</td>
<td>N0 or N1</td>
<td>M0</td>
<td>SC count &gt; 1 × 10^9/L or</td>
</tr>
<tr>
<td>IVB</td>
<td>T1-T4</td>
<td>N0-N3</td>
<td>M1: histologic visceral involvement</td>
<td></td>
</tr>
</tbody>
</table>

*This staging system does not take into account B classification in determining overall clinical stage.

Table 2. Previously reported incidences of large cell transformation in cutaneous T-cell lymphoma, using the diagnostic criterion of large cells comprising more than 25% of total lymphoid infiltrate

<table>
<thead>
<tr>
<th>First author (y)</th>
<th>Cutaneous T-cell lymphoma, n</th>
<th>Transformation, n</th>
<th>Transformation rate, %</th>
<th>Follow-up from diagnosis of large cell transformation, mo [median (range)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salhany5 (1988)</td>
<td>92</td>
<td>17</td>
<td>18</td>
<td>29 (1-72)</td>
</tr>
<tr>
<td>Greer6 (1990)</td>
<td>113</td>
<td>22</td>
<td>19</td>
<td>27 (1-72)</td>
</tr>
<tr>
<td>Vergier8 (2000)</td>
<td>419</td>
<td>45</td>
<td>11</td>
<td>26.5 (1-144)</td>
</tr>
<tr>
<td>Analogun (current study)</td>
<td>358</td>
<td>22</td>
<td>6.1</td>
<td>27 (1-348)</td>
</tr>
</tbody>
</table>
log-rank test. OS was calculated from the date of diagnosis of advanced-stage disease. All causes of death were included in the survival analysis. The following characteristics were evaluated for prognostic significance by univariate analysis: age, sex, date of diagnosis, clinical stages at first diagnosis of MF/SS and at diagnosis of ASD, tumor (T) stages at first diagnosis and at diagnosis of ASD, disease progression, presence or absence of LCT, and CD30 expression in large cells. A $P$ value of .05 was considered to be statistically significant.

## Results

### Patient characteristics

The median follow-up time for the entire cohort of 297 MF/SS patients was 4.4 years (range, 0.1-31 years). Ninety-two patients with advanced-stage MF/SS were identified. Of these, 46 patients have died; 39 deaths (85%) were disease related (disease progression, complication of treatment, or infection), 5 were unrelated to the disease (11%), and cause of death was unknown in 2 patients (4%).

The clinical characteristics of these patients, including T stage and clinical stage, are summarized in Table 3. The median age at initial diagnosis of MF/SS was 60 years, and 63 years at diagnosis of ASD. The female/male ratio was 1.14.

It is well recognized that patients may experience symptoms of CTCL for months or even years before a biopsy-proven diagnosis is made. Forty-eight patients reported having lesions or symptoms for a minimum of 2 months before diagnosis of MF/SS; among these patients, the median time from first symptoms to biopsy-proven diagnosis was 3 years (range, 0.2-40 years). Sixty-two patients (67%) were diagnosed with ASD at first presentation of their disease, whereas 30 patients (33%) were first diagnosed with ESD before progressing to an advanced stage. Of these 30 patients, 21 progressed to stage IIB (tumor) disease, 3 to stage IVA (nodal), 3 to stage IVB (visceral), and 3 to LCT. No patients progressed from ESD to erythrodermic disease (including SS). Three patients with a diagnosis of stage III (erythrodermic) disease were later diagnosed with leukemic involvement.

### Large cell transformation

LCT was diagnosed in 22 patients (13 men and 9 women). The median age at diagnosis of transformation was 64 years (range, 44-79 years). At the time of diagnosis of transformation, 4 patients had plaque lesions, 16 patients had tumor lesions, and 2 patients had erythroderma (rapidly progressive in one patient and lymph node LCT in the other). Immunophenotypic analysis showed that, in all cases, the transformed large cells were of T-cell origin (all cases were positive for the T-helper cell marker CD4). CD30 expression was observed in large cells of biopsies from 9 patients (41%). Transformation was present at the time of initial diagnosis of MF/SS in 7 patients (32%). In the remaining 15 patients (68%), median time from diagnosis of MF/SS to transformation was 2.3 years (range, 1 month to 29 years). Most patients, however, had a history of symptoms, such as rash or pruritus, before a definitive diagnosis of MF/SS was made, and the median time from first symptoms to diagnosis of transformation was 3.8 years (range, 0.4-40 years).

From the population of 297 patients with MF/SS and the population of 358 with CTCL (including MF/SS and non-MF/SS CTCL subtypes, such as lymphomatoid papulosis, etc) recorded in our database, only 22 patients were diagnosed with LCT (Table 4). The incidence of LCT in our entire CTCL population of 358 patients was 6.1%, and 7.4% in the MF/SS population. The incidence of LCT was higher in those with ASD, with LCT developing in 11 of 41 patients with stage IIB disease (27%) and 5 of 9 patients with stage IVA disease (56%) developing LCT, compared with just 1.4% of patients with stages IA, IB, and IIA disease combined.

### Outcomes

Among 92 patients with advanced-stage MF/SS, 44 patients (48%) had experienced disease progression (defined as progression from ESD, stage progression from an advanced stage, LCT, or development of leukemic involvement), with a median time to disease progression of 4.5 years (range, 1 month to 29 years).

Median OS for the 92 patients with ASD was 5 years (range, 0-13 years; Figure 1). Two-year, 5-year, and 10-year predicted OS are 66%, 49%, and 32%, respectively (Table 5).

### Predictors of outcome

Univariate analysis of potential prognostic factors are documented in Table 4. Clinical stage, tumor stage, and age were all statistically significant. According to clinical stage, the median OS of patients with stage III disease was 11 years, compared with 3 years and 1.2 years in stages IIB and IV, respectively ($P = .001$, III vs IIB vs IV; Figure 2). According to tumor stage, patients with erythrodermic (T4) disease had significantly better outcomes than patients with tumor stage (T3) disease; median OS from diagnosis of advanced-stage MF/SS for patients with T3 and T4 disease was 2.4 and 11 years, respectively ($P = .03$; Figure 3). Of interest, there was a group of patients (n = 7) who had patch/plaque-stage (T2) disease but were defined as advanced-stage based on coexistent
extracutaneous disease (thus, clinical stage IVA or IVB). These patients had a median OS of just 8 months.

Age at initial diagnosis of MF/SS was a predictive factor for outcome (Figure 4). The median age at initial diagnosis of MF/SS was 60 years. Among the patients who were younger than 60 years at the time of their first diagnosis (n = 45), median OS was 12 years, compared with just 6 years in patients who were 60 years of age or older at initial diagnosis (P = .01). Indeed, disease-specific OS was also different between patients younger than 60 years and patients 60 years of age or older at initial diagnosis (P = .049). We found no significant difference in OS between males and females from diagnosis of ASD (P = .86).

Patients with ASD who were diagnosed previously with ESD (progressors) demonstrated a less favorable outcome than patients whose first diagnosis was advanced-stage MF/SS (de novo ASD), although this difference was not statistically significant. The median OS of de novo ASD patients was 5.1 years from the diagnosis of ASD, compared with 3 years from diagnosis of ASD among patients with a prior diagnosis of ESD (P = .25). The comparison of all treatments received by patients who presented with de novo ASD and those received by patients who progressed to ASD from ESD is of interest. Treatments received before and after diagnosis of ASD were compared. Both groups contained patients with LCT. Of the patients who progressed from early-stage MF, 45% received total skin electron beam therapy and 72% received local radiotherapy to lesions, compared with only 22% of de novo ASD patients receiving total skin electron beam therapy and 22% receiving local radiotherapy. Furthermore, treatments with single-agent and multiagent chemotherapy were compared; 76% of the “progressed” group were treated with one or more types of systemic chemotherapy, compared with 52% of the “de novo ASD” group. Ultraviolet light therapies (psoralen and ultraviolet A

### Table 5. Median, 2-, 5-, and 10-year (predicted) overall survivals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Median survival, mo</th>
<th>2 years, %</th>
<th>5 years, %</th>
<th>10 years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated overall survival (entire cohort)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>From diagnosis of advanced-stage disease</td>
<td>92</td>
<td>60</td>
<td>65.8</td>
<td>48.9</td>
<td>31.8</td>
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<tr>
<td>Clinical stage (P &lt; .003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stage IIB</td>
<td>42</td>
<td>36</td>
<td>61.0</td>
<td>39.4</td>
<td>23.4</td>
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<tr>
<td>Stage III</td>
<td>36</td>
<td>132</td>
<td>83.9</td>
<td>67.8</td>
<td>53.9</td>
</tr>
<tr>
<td>Stages IVA and IVB</td>
<td>12</td>
<td>14.5</td>
<td>25</td>
<td>12.5</td>
<td></td>
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<tr>
<td>Tumor (T) stage (P = .01)</td>
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<td></td>
<td></td>
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<tr>
<td>Patch/plaque (T2)</td>
<td>7</td>
<td>8</td>
<td>42.9</td>
<td>21.4</td>
<td></td>
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<tr>
<td>Tumor (T3)</td>
<td>46</td>
<td>29</td>
<td>55.7</td>
<td>36.7</td>
<td>21.8</td>
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<tr>
<td>Erythroderma (T4)</td>
<td>39</td>
<td>132</td>
<td>82.9</td>
<td>65.2</td>
<td>52.3</td>
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<td>Presentation (P = .25)</td>
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<tr>
<td>Advanced-stage de novo</td>
<td>62</td>
<td>61</td>
<td>72.3</td>
<td>53.0</td>
<td>32.1</td>
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<tr>
<td>Progression from early-stage</td>
<td>30</td>
<td>36</td>
<td>51.9</td>
<td>41.5</td>
<td>34.6</td>
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<tr>
<td>Age at initial diagnosis (P = .01)</td>
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<td></td>
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<tr>
<td>60 y or older</td>
<td>47</td>
<td>72</td>
<td>75.1</td>
<td>57.4</td>
<td>26.1</td>
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<tr>
<td>Younger than 60 y</td>
<td>45</td>
<td>144</td>
<td>86.1</td>
<td>72.5</td>
<td>55.9</td>
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<tr>
<td>Large cell transformation (P = .17)</td>
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<tr>
<td>No transformation</td>
<td>70</td>
<td>62</td>
<td>70.7</td>
<td>53.6</td>
<td>34.0</td>
</tr>
<tr>
<td>Transformation</td>
<td>22</td>
<td>27</td>
<td>50.6</td>
<td>32.5</td>
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<td>CD30 large cell expression (P = .19)</td>
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<td>CD30-positive large cells</td>
<td>9</td>
<td>57</td>
<td>55.6</td>
<td>41.7</td>
<td></td>
</tr>
<tr>
<td>CD30-negative large cells</td>
<td>13</td>
<td>27</td>
<td>51.9</td>
<td></td>
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<tr>
<td>Erythrodermic disease (P = .34)</td>
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<td></td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td>31</td>
<td>132</td>
<td>75.0</td>
<td>60.8</td>
<td>54.7</td>
</tr>
</tbody>
</table>

— indicates not applicable.
and narrow-band ultraviolet B) were used in 72% of the “progressed” group and in 41% of the “de novo ASD” group.

Patients with LCT appeared to have poorer outcomes than the remaining 70 patients with ASD without evidence of transformation (Figure 5); the median OS in the transformed group was 2.2 years, compared with 5.2 years in the nontransformed group ($P = .008$; Table 4). We were unable to demonstrate a difference in OS between patients with CD30-positive transformation and those with CD30-negative transformation, although patients with CD30-positive transformation tended toward a better outcome ($P = .19$; Table 4).

Among the 39 patients with erythroderma, 31 patients (79%) demonstrated leukemic involvement (SS). Of these 31 patients, 28 met the classic criteria of SS, and there were 3 patients who had monoclonality in the blood determined only by a positive T-cell receptor gene rearrangement by polymerase chain reaction technique. Two-year predicted survivals in SS and erythrodermic MF were 75% and 100%, respectively (Table 4). Conclusions regarding survival differences cannot be drawn because of small numbers of patients in both groups.

Discussion

Advanced-stage MF and SS are associated with a poorer prognosis and a more aggressive clinical course than ESD. In this study, we presented the results of a long-term retrospective cohort study of 92 patients with advanced-stage MF/SS.

The median OS was 5 years. Clinical stage and tumor stage at diagnosis were both important factors predictive of outcome, and patients with stage III disease had the best outcome, with a median OS of 11 years. At first, this may seem somewhat surprising as the reported median survival for SS is between 2 and 4 years. However, one must bear in mind that many patients with SS are classified as clinical stage IV disease if they have extracutaneous involvement, a group known to have poor outcome. Indeed, in our analysis, patients with extracutaneous (stage IV) disease had the poorest outcomes.

Similarly, we found a significantly superior OS in patients with erythrodermic (T4) disease compared with T3 (tumor stage) disease ($P = .02$). However, this observation has not been seen by others. It is not possible to definitively explain this discrepancy between investigators, but it is probable that there are other influencing factors, such as the proportion of patients who have extracutaneous disease in association with erythroderma in the patient populations.

Patient age at initial diagnosis of MF/SS was found to be predictive of OS, and this was true also for disease-specific OS. The reason for this is not known but could possibly be the result of poorer immune surveillance in the older population, or poorer tolerance of therapies, which are more aggressive in ASD than in ESD. This finding should be considered in future studies of novel therapies of CTCL.

From time of diagnosis of advanced-stage disease, patients who presented with de novo ASD appeared to have a better outcome (from that time point) than those with a prior diagnosis of ESD (of note, for those patients with ESD who later progressed to ASD, their median OS from initial MF diagnosis was 12 years). It is not possible to fully explain the reasons behind this phenomenon. We postulate that patients with de novo ASD may be less probable to harbor multidrug resistance. Our analysis of drug exposure between the de novo ASD and progressed groups did show that patients who progressed from early-stage MF received more treatment during their disease course. One reason may be that patients who develop stage progression despite therapy may develop tumor drug resistance. An alternative hypothesis is that those who present with de novo ASD may have inherently less aggressive or proliferative tumors. We think this issue warrants further study.

LCT is one of the most feared complications of MF, with our patients having a median survival of only 2 years. Previous studies, with comparable follow-up times, report the incidence of LCT in
the excellent outcome of stage I disease, it is probable that, with
reflects the prevalence of MF in the community. Nonetheless, given
proportion of patients with ESD in our database and probably
95% of patients who attend our Cutaneous Lymphoma Clinic are
patient populations in the various databases. In general, more than
50% in patients with stage IV disease. This is very useful
information for providing prognostic information to patients. The
difference between our relatively low incidence of transformation
and those of previous studies is probably the result of different
patient populations in the various databases. In general, more than
95% of patients who attend our Cutaneous Lymphoma Clinic are
referred by community dermatologists; this translates to a high
proportion of patients with ESD in our database and probably
reflects the prevalence of MF in the community. Nonetheless, given
the excellent outcome of stage I disease, it is probable that, with
longer follow-up, the incidence of LCT in our population will rise.

Finally, this study highlights some of the inadequacies of the
“current” clinical staging system. These include the substantially
better outcomes of patients with stage III disease than of patients
with stage IIB disease and the need to better subclassify patients
with erythrodermic MF into patients with nodal/visceral/blood
involvement. Our findings provide further support for revisions to
the current TNM staging system for MF/SS according to the recent
the International Society for Cutaneous Lymphomas and the
Cutaneous Lymphoma Task Force of the European Organization of
Research and Treatment of Cancer staging proposal.14

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Authorship
Contribution: S.O.A. collected and analyzed data, performed
statistical analysis, and wrote the manuscript; H.M.P. designed
research and wrote the manuscript; J.N. collected and analyzed data
and performed research; S.L. analyzed data; G.F.R. designed
research and contributed data; O.B. collected data; and C.M.
designed research and contributed data.

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