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Survival, disease progression and prognostic factors in elderly patients with mycosis fungoides and Sézary syndrome: a retrospective analysis of 174 patients

E. Lebowitz^{#1}, S. Geller^{#1,2}, E. Flores², M. Pulitzer^{1,3}, S. Horwitz^{1,4}, A. Moskowitz^{1,4}, M. Kheterpal^{1,2,5}, and P. L. Myskowski^{1,2}

¹Weill Cornell Medical College, New York, NY, USA

²Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

³Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁴Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer, New York, NY, USA

⁵Department of Dermatology, Duke University, Durham, NC, USA

These authors contributed equally to this work.

Abstract

Background: Advanced age at diagnosis is considered a poor prognostic factor in mycosis fungoides (MF) and Sézary syndrome (SS).

Objective: To evaluate the outcomes and prognostic factors in patients diagnosed at an advanced age (≥ 65 years) with MF/SS.

Methods: Survival, progression rates and various clinical and histopathological variables were studied in a group of 174 elderly patients diagnosed with MF/SS between 1992 and 2015 at a single referral cancer center in the United States. Kaplan–Meier estimates were used to determine survival and progression and Cox proportional hazards regression univariate and multivariate models were used to identify prognostic factors.

Results: Of 174 elderly patients, 76.4% were diagnosed with early-stage (clinical stages IA–IIA) and 23.6% with late-stage MF/SS (IIB–IV). Advanced age was associated with poor overall

Correspondence: Shamir Geller, MD, Dermatology Service, Memorial Sloan Kettering Cancer Center, 16 East 60th Street, New York, NY 10022, USA; Tel: (646) 888 6032, shamirgeller@gmail.com.

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Conflicts of interest: Dr. Horwitz has received consulting fees from or is on an advisory board for Celgene, Infinity Pharmaceuticals, Kyowa Hakko Kirin, Seattle Genetics Inc, Spectrum Pharmaceuticals, Millennium Pharmaceuticals Inc, HUYA Bioscience, and Forty Seven; and has received research funding from Celgene, Infinity Pharmaceuticals, Kyowa Hakko Kirin, Seattle Genetics Inc, Spectrum Pharmaceuticals, Millennium Pharmaceuticals Inc, and ADC Therapeutics. Dr. Moskowitz has received research support from Seattle Genetics Inc and has received honorarium from Seattle Genetics and Takeda. Dr. Myskowski has received research support from Allos Therapeutics, Ligand Pharmaceuticals (Valeant), Schering-Plough Corporation, U.S. Bioscience (Medimmune), Bristol Myers Squibb, Merck, Orthobiotech, Genmab, Millenium, Janssen. Dr. Geller, Ms. Lebowitz, Ms. Flores, Dr. Pulitzer, and Dr. Kheterpal have no conflicts of interest to declare.

survival, but not with disease-specific survival (DSS) or progression free survival (PFS). Gender, increasing clinical stage, T and B classifications, elevated lactate dehydrogenase (LDH) levels, and development of large cell transformation (LCT) were significant predictors of poor survival or disease progression. Patients with early-stage MF and <10% total skin involvement (T1 classification) or patches only disease (T1a/T2a) showed better PFS with no observed disease-specific mortality. Folliculotropic MF was associated with poor DSS in patients with early-stage disease.

Conclusions: Older age at diagnosis of MF/SS does not predict worse disease-specific outcomes. Elderly patients with early-stage disease, specifically involving less than 10% of the skin surface with patches but without plaques or folliculotropism, have an excellent prognosis. However, the development of LCT is a strong prognostic indicator of poor survival in elderly patients with MF/SS.

Introduction

The incidence of cutaneous T-cell lymphoma (CTCL) increases with age and peaks in the elderly population with an incidence rate of 36 CTCL cases per million persons in patients over the age of 70 in the United States (US).¹ Mycosis fungoides / Sézary syndrome (MF/SS) is the most common type of primary CTCL. The median age of diagnosis of MF/SS is usually 55–60 years,² and the incidence of MF rises relatively sharply with age.³ Advanced age has been shown to be associated with a more advanced clinical stage at presentation,⁴ as well as with worse overall survival (OS),⁵ disease-specific survival (DSS) and greater risk for disease progression.^{6–9} The decline of immune system function with age has been suggested to contribute to the high incidence, advanced disease at presentation, and poor outcomes in elderly patients with MF/SS.¹⁰

Treatment selection in elderly patients with MF/SS is often challenging due to comorbidities, multiple concurrent medications, impaired functional ability and increased risk of treatment-associated toxicities in this population.¹¹ Therefore, identification of factors that are relevant to outcome and survival is of specific importance in this age group and may lead to better management and improved survival. A Cutaneous Lymphoma International Prognostic index (CLIPi) has been recently developed for early- and late-stage MF/SS and it includes age over 60 years at diagnosis as a significant adverse prognostic factor; however, CLIPi utility in elderly patients is unclear.¹² The aim of this study was to evaluate the outcomes in a retrospective cohort of patients who were diagnosed with MF/SS at the age of 65 and older and to evaluate prognostic factors in this age group.

Patients and Methods

Patient selection and clinical parameters

We retrospectively searched our institutional cancer registry and pathology database between the years 1992–2015 for patients who were diagnosed with MF/SS at the age of 65 or older and were followed at Memorial Sloan Kettering Cancer Center. We included patients with a diagnosis of MF/SS which was confirmed clinically and pathologically at our institution. Patients were excluded if clinical records were incomplete or if they were followed at our

institution for less than a year, unless they died within that period. This study was approved by the Institutional Review Board.

Medical records were retrospectively reviewed for the following parameters: age at diagnosis, sex, (self-identified) ethnicity, duration between symptom onset and diagnosis, clinical and TNMB classification stage at the time of diagnosis based on the International Society for Cutaneous Lymphoma and Cutaneous Lymphoma Task Force of the European Organization for the Research and Treatment of Cancer (EORTC) classification,¹³ presence of plaques and/or patches on physical exam, and lactate dehydrogenase (LDH) levels. Patients were assigned to the following age groups: 65–74, 75–84, and 85. Pathology reports at diagnosis were reviewed for confirmation of folliculotropic MF (FMF) and large cell transformation (LCT). Follow-up records were reviewed for development of LCT and for the following outcomes: progression to a higher clinical MF/SS stage, death from any cause or due to MF/SS.

Statistical Analysis

The date of the first diagnostic biopsy was considered as the date of diagnosis. Overall survival (OS) was calculated from the date of diagnosis to death from any cause or last follow-up. Disease-specific survival (DSS) was calculated from date of diagnosis to death from MF/SS, death from another cause, or last follow-up. Progression free survival (PFS) was defined as time from diagnosis to progression to a more advanced clinical stage or death from MF/SS disease. Univariate and multivariate analyses of survival and progression risk for prognostic factors were performed using Cox proportional hazards model. χ^2 test was used to compare proportions and t test or Wilcoxon test were used to compare numeric data. Kaplan-Meier curves were calculated for OS, DSS and PFS and log-rank tests were used to assess equality. All tests were 2-sided and P-value less than 0.05 was considered statistically significant. Statistical analyses were performed using Stata software (version 12.1; StataCorp LP, Huston, TX, USA).

Results

Patients' characteristics

A total of 174 elderly patients with MF/SS, 76 females (43.7%) and 98 males (56.3%), met the inclusion criteria and were included in this study. Mean age at diagnosis was 73 years (range 65–100). Of the 174 patients, 133 (76.4%) were diagnosed with early-stage MF/SS (clinical stages IA-IIA); 41 patients (23.6%) were diagnosed with late-stage disease (IIB-IVB). None of the patients in our study had metastatic disease (M1) at presentation. The mean time from onset of skin eruption to biopsy-proven MF/SS was 4.6 years, with no significant difference between patients with late- versus early-stage disease ($p=0.85$).

Disease progression and survival rates

Mean duration of follow-up from diagnosis was 4.5 years (median 3 years, range 0.5–22 years). Disease progression to a higher clinical stage occurred in 18 patients (10.3%). Overall, 52/174 patients (29.9%) died and 15 deaths (8.6%) were attributed to MF/SS. Of 133 patients with early-stage MF/SS, 14 (10.5%) experienced disease progression after a

mean period of 1.8 years (range 0.4 to 11 years) and 5/133 (3.8%) died from disease. Of 41 patients with late-stage MF/SS, 12 (29.3%) progressed after a mean period of 1.1 years (range 0.8 to 4 years) and disease-specific death rate was 10/41 (24.4%). Elderly patients who were diagnosed with late-stage disease had significantly lower OS and DSS compared to elderly patients who had early-stage disease at diagnosis as shown in Figure 1.

Prognostic factors

In a univariate analysis of the entire cohort, OS was significantly worse across the age groups and no significant differences were found for DSS and PFS (Table 1). Increased age was confirmed to be independently associated with OS and not with DSS or PFS in a multivariate analysis.

OS, DSS, and PFS were significantly different across clinical stage. OS and PFS differed significantly across T classifications, and OS and DSS across B classifications in a univariate analysis. Elevated LDH was significantly correlated with poor outcomes. Univariate analysis of the entire cohort showed no differences in OS, DSS, or PFS based on the presence of FMF.

LCT at the time of diagnosis did not have significant impact on survival. The development of LCT during follow-up, however, was a negative prognostic factor for OS [hazard ratio (HR) = 1.72, 95% confidence interval 1.80–7.97, $p < 0.001$] and DSS [HR=12.27, 4.25–35.39, $p < 0.001$] in univariate analysis. Multivariate analysis was performed for OS and showed better OS in females and worse OS was independently associated with increasing T classification, elevated LDH, B1 compared to B0 classification and development of LCT. Multivariate analysis for PFS showed independent association of increasing T classification with PFS and not with B classification or elevated LDH.

Prognostic factors in early- and late-stage disease

Prognostic factors were analyzed separately for early- and late-stage MF/SS patients and are shown in Table 2. Increasing age was significantly associated with reduced OS but not with DSS or PFS in early-stage disease and was of no prognostic significance in late-stage patients. In a multivariate analysis, increasing age was independently associated with OS in the early-disease group and for patient 85 in the late-disease group.

In the early-stage MF/SS group, patients with T2 classification (patches or plaques covering 10% of the skin surface) had worse PFS than patients with T1 classification (<10% involvement). Presence of plaques (T1b/T2b¹³) was significantly associated with worse PFS compared to patches only. No cases of MF/SS-associated deaths were observed in patients with early-stage disease and T1 classification or patch-only disease (T1a/T2a) (Figure 2a). FMF was associated with poor DSS in early-stage MF/SS (Figure 2b). In the late-stage group, elevated LDH was significantly associated with poor OS. Gender, N and B classifications were not associated with survival or progression in univariate analysis.

In multivariate analysis for OS in the early-stage group, T2 classification was associated with worse OS compared to T1. In the late-stage group, female patients had better OS and

B1/B2 classification was associated with worse OS compared to B0, while elevated LDH was no longer associated with worse OS in a multivariate analysis.

Discussion

Disease progression in MF usually occurs as a slow evolution from patches and plaques to tumors and to extracutaneous disease with possibly fatal outcomes. While the vast majority of patients with early-stage MF will not progress to late-stage disease, such progression may arise in 5–10% of patients with clinical stage IA and in 17–39% with stage IB.⁷ Prognostic factors outside the staging system may assist in the management of MF/SS by identifying patients with a potentially poor prognosis.

Older age is a known risk factor for MF/SS development and has been reported as associated with disease progression and poor outcomes.^{5,9} It has been debated whether it is an independent adverse prognostic factor¹⁴ or whether older patients have a propensity to present with advanced disease stages.^{4,8,15} The association between older age and OS was reported in several single-center studies,^{8,9,15–23} collaborative international cohorts,²⁴ and in United States Surveillance, Epidemiology and End Results (SEER) dataset-based studies.^{5,3} The association between advanced age and DSS has been less consistent. Several cohort studies that reported on a significant association between old age and OS failed to do so for DSS.^{17,19,25} In other studies older age was correlated with poor DSS in univariate analysis but not in multivariate analysis.^{7,22} In our study in elderly patients, advanced age was associated with reduced OS, but not with DSS or PFS in both univariate and multivariate analysis.

We observed that 76% of the patients who were diagnosed at the age of 65 years or older were diagnosed with early-stage MF/SS, mainly clinical stages IA (44%) and IB (31%). As expected, the elderly patients with late-stage disease had significantly worse OS, DSS and PFS compared to those with early-stage disease.

No MF/SS-associated mortality occurred among elderly patients who presented with clinical stage IA, <10% total skin surface involvement (T1 classification), or early-stage patch disease without plaques (T1a/T2a), and progression of disease was rarely seen in these patients. In early-stage disease, T2 classification and plaques were found to have prognostic implications for risk of progression in univariate analysis and T2 classification association was also confirmed in multivariate analysis. FMF was shown to be a predictor of poor DSS among elderly patients with early-stage MF/SS, however FMF was not associated with worse outcomes when the entire cohort was analyzed. The latter finding can be supported by recent reports in the literature on the heterogeneous outcomes of FMF and the existence of folliculotropic subtypes that may have a favorable prognosis.^{23,26}

In the elderly patients with late-stage disease, elevated LDH was identified in univariate analysis along with male gender and B1/B2 classifications that were identified in multivariate analysis - all were associated with reduced OS and none was found to have prognostic implications for DSS or PFS in the late-stage group.

Large cell transformation (LCT), defined as >25% large cells of atypical lymphocytes on histopathology, has been shown to be a poor prognostic factor in MF/SS.¹⁴ Our analysis showed that the development of LCT was strongly associated with poor survival in MF/SS in both univariate and multivariate analysis. Patients who presented with LCT at diagnosis did not experience worse outcomes, and we have previously shown that patients presenting with LCT at diagnosis have better survival than those who initially present with a small cell phenotype and later develop LCT.²⁷

Numerous studies have attempted to validate prognostic factors and tools to be used in MF/SS.¹⁴ The recently developed prognostic index (CLIPi¹²) includes five factors that were found to be associated with worse OS in early-stage disease: age >60 years, male sex, presence of plaques, FMF and lymph node stage N1/Nx. For advanced-stage, the CLIPi prognostic factors were determined to be age >60 years, male sex, nodal stage N2/N3, blood stage B1/B2 and visceral involvement.¹² While age and gender are key factors in CLIPi, we were not able to confirm the prognostic implications of age and gender for DSS or PFS in our study. Arguably, the association between advanced age / male gender and OS may be influenced by factors unrelated to MF/SS. Of the other CLIPi parameters, presence of FMF predicted poor DSS and presence of plaques predicted worsening PFS and DSS in elderly patients with early-stage disease. Our study did not observe any prognostic implications for lymph node stage, although low numbers of events may have impacted the results. Visceral involvement could not be evaluated as none of the patients in our cohort presented with such dissemination. B1/B2 classification was associated with OS in late-stage disease. Further prospective multi-center studies of larger patient cohorts are ongoing and are expected to further identify adverse prognostic factors and lead to reliable prognostic indexes in MF/SS.

The retrospective nature of the data collection is a limitation of this study. Our cohort consisted of patients seen at a single tertiary cancer center, and although our study population consisted of a heterogeneous group of elderly patients with early- and late-stage MF/SS, a referral bias might exist towards patients with more advanced disease. However, in an elderly population, the bias might alternatively be towards patients who have lower disease burden and better functional ability to reach a tertiary referral center.

In summary, our results show that advanced age is not associated with poor DSS or PFS in patients who are diagnosed with MF/SS older than 65 years. Elderly patients with early-stage disease who present with <10% involvement of the total skin surface or with patch only disease (T1a, T1b, T2a) have an excellent prognosis and may be followed and treated similar to younger patients with early-stage disease. Patients with early-stage MF, who are diagnosed with presence of FMF or plaque disease should be monitored carefully for disease progression. In addition, the development of LCT is significantly associated with poor survival in elderly patients with MF/SS and should be looked for during their follow-up. The development of a prospectively validated prognostic index in MF/SS will be of great aid in the management of elderly patients with MF/SS.

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Figure 1. Survival outcomes of elderly patients with early- and late-stage mycosis fungoides (MF). Kaplan-Meier curves for (a) Overall survival (OS) and (b) Disease-specific survival (DSS)

Figure 2. Disease specific survival (DSS) of elderly patients with early-stage disease. Kaplan-Meier curves for (a) plaque disease and (b) folliculotropism.

Univariate analysis of overall, disease-specific, and progression-free survival of elderly patients with MF/SS (clinical stages IA-IVB, total = 174 patients)

Table 1

Characteristic	N (%) Total = 174 patients	Overall survival			Disease-specific survival			Progression-free survival		
		HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Gender										
Male	98 (56)	1.00			1.00			1.00		
Female	76 (44)	1.58	(0.91-2.75)	0.103	3.10	(1.04-9.25)	0.042	2.01	(0.92-4.41)	0.081
Age										
65 – 74	116 (67)	1.00			1.00			1.00		
75 – 84	48 (27)	2.72	(1.51-4.88)	0.001	1.95	(0.63-5.98)	0.244	1.12	(0.44-2.85)	0.812
85	10 (6)	5.26	(2.11-13.08)	0.000	4.04	(0.85-19.29)	0.080	3.20	(0.93-11.04)	0.066
Race										
White	152 (87)	1.00			1.00			1.00		
African American	15 (9)	0.86	(0.31-2.40)	0.772	-	-	-	0.79	(0.29-3.33)	0.740
Clinical Stage										
IA	76 (44)	1.00			NA	-	-	1.00		
IB	54 (31)	2.25	(1.02-4.96)	0.045	1.00			8.75	(1.92-39.26)	0.005
IIA	3 (2)	5.31	(1.13-24.94)	0.034	-	-	-	18.94	(1.70-210.68)	0.017
IIIB	9 (5)	7.05	(2.13-23.33)	0.001	3.99	(0.71-22.25)	0.115	10.34	(1.45-74.02)	0.020
IIIA + IIIB	11 (6)	5.60	(1.89-16.60)	0.002	4.82	(1.07-21.71)	0.040	22.77	(4.38-118.4)	0.000
IVA	21 (12)	14.67	(6.34-33.93)	0.001	5.74	(1.52-21.73)	0.010	17.40	(1.45-74.05)	0.001
Early stage (IA-IIA)	133 (76)	1.00			1.00			1.00		
Late stage (IIIB-IVB)	41 (24)	5.91	(3.32-10.52)	0.000	12.03	(3.72-38.92)	0.000	4.03	(1.85-8.79)	0.000
T classification										
T1	75 (43)	1.00			NA	-	-	1.00		
T2	60 (35)	2.40	(1.12-5.14)	0.024	1.00			8.85	(2.00-39.24)	0.004
T3	9 (5)	6.35	(1.94-20.81)	0.002	3.48	(0.66-18.29)	0.141	9.89	(1.39-70.62)	0.022
T4	30 (17)	9.08	(4.11-20.06)	0.000	4.34	(1.36-13.87)	0.013	18.08	(3.88-84.16)	0.000
N classification										
N0	156 (90)	1.00			1.00			1.00		

Characteristic	N (%) Total = 174 patients	Overall survival			Disease-specific survival			Progression-free survival		
		HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Nx	6 (3)	1.51	(0.46-4.94)	0.492	1.87	(0.24-14.81)	0.551	0.78	(0.10-5.84)	0.806
N1	8 (5)	3.71	(1.55-8.87)	0.003	2.08	(0.26-16.42)	0.487	0.91	(0.12-6.83)	0.929
N2/N3	4 (2)	1.65	(0.40-6.87)	0.490	2.90	(0.37-22.76)	0.311	1.30	(0.17-9.71)	0.797
B classification										
B0	146 (84)	1.00			1.00			1.00		
B1	9 (5)	3.12	(1.10-8.87)	0.033	7.76	(1.59-37.80)	0.011	5.24	(1.74-15.79)	0.003
B2	18 (10)	2.62	(1.38-4.99)	0.003	4.15	(1.35-12.77)	0.013	1.60	(0.59-4.38)	0.359
Folliculotropic MF										
No	165 (95)	1.00			1.00			1.00		
Yes	9 (5)	1.32	(0.47-3.68)	0.598	2.28	(0.51-10.28)	0.283	1.37	(0.32-5.85)	0.667
LCT at presentation										
No	170 (98)	1.00			1.00			1.00		
Yes	4 (2)	1.72	(0.24-12.61)	0.591	4.84	(0.63-37.31)	0.130	2.22	(0.30-16.46)	0.435
LDH										
Normal	90 (52)	1.00			1.00			1.00		
Elevated	40 (23)	5.72	(3.02-10.85)	0.000	9.76	(2.81-33.90)	0.000	2.98	(1.34-6.66)	0.008

B, blood; HR, hazard ratio; LCT, large-cell transformation; LDH, lactate dehydrogenase; MF, mycosis fungoides; N, node; T, tumor

Table 2

Univariate analysis of overall, disease-specific, and progression-free survival in elderly patients with early-stage and late-stage MF/SS

<i>Early-stage MF (clinical stages IA-IIA, n = 133)</i>									
Characteristic	Overall survival			Disease-specific survival			Progression-free survival		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Gender									
Male	1.00			1.00			1.00		
Female	1.31	(0.61-2.81)	0.494	1.39	(0.22-8.64)	0.721	1.27	(0.44-3.68)	0.660
Age									
65 – 74	1.00			1.00			1.00		
75 – 84	2.99	(1.35-6.62)	0.007	1.30	(0.13-12.57)	0.820	0.69	(0.15-3.13)	0.631
85	8.69	(2.40-31.50)	0.001	10.44	(0.98- 110.68)	0.052	2.34	(0.30-18.41)	0.419
T classification									
T1	1.00			NA	-	-	1.00		
T2	2.16	(0.99-4.69)	0.052	-	-	-	8.22	(1.84-36.76)	0.006
N classification									
N0	1.00			1.00			1.00		
N1/Nx	6.81	(0.85-54.58)	0.071	-	-	-	-	-	-
Folliculotropic MF									
No	1.00			1.00			1.00		
Yes	2.18	(0.64-7.36)	0.211	11.46	(1.75-74.93)	0.011	4.37	(0.96-19.97)	0.057
Plaques									
No	1.00			NA	-	-			
Yes	1.50	(0.71-3.17)	0.292	-	-	-	3.26	(1.01-10.48)	0.048
<i>Late-stage MF (clinical stages IIB-IVB, n = 41)</i>									
Characteristic	Overall survival			Disease-specific survival			Progression-free survival		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Gender									
Male	1.00			1.00			1.00		
Female	1.24	(0.53-2.90)	0.624	3.00	(0.63-14.20)	0.166	2.43	(0.65-9.05)	0.184
Age									
65 – 74	1.00			1.00			1.00		
75 – 84	1.47	(0.62-3.47)	0.379	1.36	(0.36-5.08)	0.649	1.16	(0.33-4.14)	0.819
85	1.37	(0.38-4.95)	0.632	0.85	(0.10-7.34)	0.885	2.22	(0.43-11.47)	0.339
N classification									
N0/Nx/N1	1.00			1.00			1.00		
N2/N3	0.78	(0.18-3.36)	0.742	0.95	(0.12-7.60)	0.958	0.81	(0.10-6.41)	0.842
B classification									
B0	1.00			1.00			1.00		

<i>Early-stage MF (clinical stages IA-IIA, n = 133)</i>									
Characteristic	Overall survival			Disease-specific survival			Progression-free survival		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
B1/B2	1.70	(0.70-4.15)	0.244	1.80	(0.46-6.98)	0.397	0.69	(0.20-2.38)	0.553
LDH									
Normal	1.00			1.00			1.00		
Elevated	3.53	(1.20-10.44)	0.022	6.77	(0.85-53.65)	0.070	3.36	(0.73-15.38)	0.119

B, blood; HR, hazard ratio; LDH, lactate dehydrogenase; MF, mycosis fungoides; N, node; T, tumor