Title

Tumor stage mycosis fungoides: a single-center study on clinicopathologic features, treatments, and patient outcome

Permalink

https://escholarship.org/uc/item/1q15b903

Journal

Authors

Patrawala, Samit A
Broussard, Karen C
Wang, Li
et al.

Publication Date

2016

DOI

10.5070/D3225030939

Copyright Information

Peer reviewed

Original

Tumor stage mycosis fungoides: a single-center study on clinicopathologic features, treatments, and patient outcome

Samit A Patrawala MD[1], Karen C Broussard MD[2], Li Wang MS[3], John A Zic MD[2]

Dermatology Online Journal 22 (5): 2

[1]Department of Dermatology, Emory University, Atlanta, GA

[2]Vanderbilt Division of Dermatology, Nashville, TN

[3]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN

Correspondence:

John A. Zic, M.D.
Professor of Medicine/Dermatology
Vanderbilt University School of Medicine
719 Thompson Lane, Suite 26300
Nashville, TN 37204-3609
Tel. (615)-322-0845, Fax (615) 343-2591
Email: john.zic@vanderbilt.edu

Abstract

Background: Tumor stage mycosis fungoides (MF) is a subtype of cutaneous T-cell lymphoma (CTCL). Tumor stage MF is rarely curable. Treatment is aimed towards controlling the disease and minimizing side effects from therapy.

Objective: To characterize clinicopathologic features of tumor stage MF and the impact of clinical characteristics and treatment modalities on patient outcome.

Methods: A retrospective chart review was conducted on 39 patients with tumor stage MF followed at Vanderbilt University between July 1995 and July 2010.

Results: The median age of diagnosis was 61 years (IQR: 54-70). Sixty-nine percent of the patients were male (27/39). The median follow-up time was 13.6 months (IQR: 5.5-35.9). Among the patients younger than 60 years at the time of initial diagnosis (n = 19), median overall survival (OS) was 7.0 years (95% CI: 2.1-17.9), compared with 3.3 years (95% CI: 2.4-9.3) in patients who were 60 years or older at initial diagnosis. Ten patients with T1/T2 stage at diagnosis had median OS of 5.0 years (95% CI 3.2-7.0). Twenty-eight patients with T3 stage at diagnosis had median OS of 5.8 years (95% CI 2.4-14.2). Median OS for patients with large cell transformation (LCT) and without LCT was 3.3 and 7.7 years, respectively.

Limitations: This is a retrospective study with the bias of a tertiary-care referral center.

Conclusion: Although LCT and older age at diagnosis were not statistically significant negative prognostic indicators of OS, there was a trend towards statistical significance for LCT. Clinical stage at diagnosis may not affect OS in patients who develop tumor stage MF.

Abbreviations:

CTCL: cutaneous T-cell lymphoma
MF: mycosis fungoides
LCT: large cell transformation
OS: overall survival
JZ: John A. Zic, M.D
ISCL: International Society for Cutaneous Lymphomas
EORTC: European Organization of Research and Treatment of Cancer
TTF: time to treatment failure
PGA: Physician's Global Assessment of Clinical Condition
CR: complete response
PR: partial response
PD: progressive disease
IQR: Interquartile Range
CI: confidence interval
LEBRT: localized electron beam radiation therapy
TSEBRT: total skin electron beam radiation therapy
ECP: extracorporeal photopheresis
PUVA: Phototherapy with psoralen plus ultraviolet A
SS: Sézary syndrome

Introduction

Cutaneous T-cell lymphomas (CTCL) are a subset of indolent non-Hodgkin lymphomas of T-cell origin characterized by primary skin involvement. Mycosis fungoides (MF) accounts for the majority of CTCL with an incidence of approximately six cases per million per year, accounting for about 4 percent of all cases of non-Hodgkin lymphoma [1, 2]. Clinical investigations, treatment approaches, and prognosis are determined by stage of disease at diagnosis [3, 4, 5]. While patients with early patch or plaque stage MF generally run an indolent course with a 10-year disease-specific survival (DSS) of over 80%, patients developing skin tumors or extracutaneous disease have a reduced 10-year DSS of 42% and <20%, respectively [6, 7]. Tumor stage MF typically requires systemic or radiation therapy and there have been no randomized controlled trials comparing different therapies head to head. In addition, the literature regarding large cell transformation (LCT) in CTCL has been inconsistent. We report a series of 39 patients with tumor stage MF to better characterize clinical features and treatment modalities affecting disease course and overall survival (OS).

Methods

Patient Selection:

Following institutional review board approval, a retrospective chart review was conducted on 39 patients with tumor stage MF followed at the Vanderbilt University Cutaneous Lymphoma Clinic between July 1995 and July 2010. Patients were identified by analysis of the Vanderbilt cutaneous lymphoma database, containing over 500 patients with CTCL presenting over the 15-year period. All patients were evaluated by a single physician (JZ), had biopsy proven MF, and were staged according to the new criteria proposed by the ISCL and EORTC [8, 9]. Patients met study inclusion criteria if they developed tumors at any point in their clinical course. A tumor of CTCL was defined as a dome-shaped nodule greater than one centimeter in size. No patients had coexisting primary anaplastic large cell lymphoma or lymphomatoid papulosis. This study was approved by the Vanderbilt University Medical Institutional Review Board.

Definitions:

Time to treatment failure (TTF) was defined as time from treatment start date to the date of treatment failure. A treatment was considered a failure if the physician discontinued the treatment due to progression of disease, lack of response, side effects, or cost

of drug limiting patient access to medication. Follow-up time was defined as time from the first CTCL clinic visit to the last documented clinic visit. If the patient took the same treatment multiple times, only the first treatment trial was counted.

By following the Physician's Global Assessment of Clinical Condition (PGA), a complete response (CR) was defined as no evidence of disease, including cutaneous and extracutaneous manifestations, for a minimum of 4 weeks. According to PGA, partial response (PR) was defined as greater than 50% clearing of lesions for a minimum of 4 weeks. Stable disease was defined as no significant change in disease. Progressive disease (PD) was defined as greater than 25% appearance of new skin lesions, development of extracutaneous involvement, or progression to more advanced stage.

The diagnosis of LCT was made based on MF histology on skin biopsy and large cells exceeding 25% of the total lymphoid infiltrate [10]. Lymphocytes were considered large cells if they were at least 4 times greater in size than a small lymphocyte. OS was estimated using the Kaplan-Meier method and was defined as time from the date of diagnosis to the date of death [11]. At June 1, 2011, patients were censored if they were alive at the conclusion of the study.

Baseline and Study Tests:

Evaluation at presentation included: medical history, complete physical examination, histopathology evaluation of skin biopsy specimens, skin and blood immunophenotyping (CD2, CD3, CD5, and CD7) full blood cell count with differential, renal and liver function tests, lipid profile, and thyroid-stimulating hormone, and free thyroxine levels. Computed tomography scans and lymph node biopsy of clinically abnormal lymph nodes were also performed when indicated.

Statistical Analysis:

Descriptive statistics were calculated as the median with interquartile range (IQR) for continuous variables. The two numbers comprising the IQR represent the lower and upper quartile respectively, which encompasses the middle 50% range. For categorical variables, frequencies and percentages, as well as the point estimate with 95% confidence interval (CI) were calculated. The Kaplan-Meier method was used to estimate the OS [11]. All statistical analyses were performed using open source R statistical software (version 2.12.0, Vienna, Austria).

Results

Clinical Characteristics and follow-up data:

Thirty-nine patients met study inclusion criteria. Patients' baseline characteristics are summarized in Table 1. The median age at diagnosis was 61 years (IQR: 54-70). Sixty-nine percent of the patients were male (27/39). The majority of patients were Caucasian (95%). The median interval between onset of symptoms and diagnosis was three years (IQR: 0.7-10.0). The median follow-up time was 13.6 months (IQR: 5.5-35.9). The majority of patients (72%) had stage IIB at diagnosis. Only one patient had erythroderma. During the 15-year study period, 27 (69%) patients died with 4 patients lost to follow up (10%). Characteristic clinical photos and histopathology of patients in the study are illustrated in Figures 1-3.

**Table 1.** Demographic characteristics of study population

	N	Frequency (%)	Median, (Inner quartile range)
Age at Diagnosis	39		61, (54-70)

Gender
  Female
  Male
	39
	12
	27
		
		31
		69	

Race
  Caucasian
  African American
	39
	37
	2
		
		95
		5	

Duration of skin findings prior to CTCL diagnosis (months)			36, (8-120)

| Current Status	39		
Alive free of disease	2	5	
Alive with disease	6	15	
Deceased	27	69	
Lost to follow-up	4	10	
Total # of treatments			5, (3-9)
Clinical Stage at Diagnosis	39		
IA	3	8	
IB	7	18	
IIB	28	72	
IVA1	1	3	
Follow-up time (months)			14, (6-36)

N: # of patients

Figure 1. Tumor Stage Mycosis Fungoides. Characteristic ulcerated tumors seen in study population.
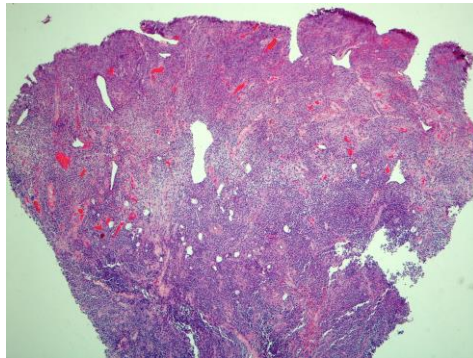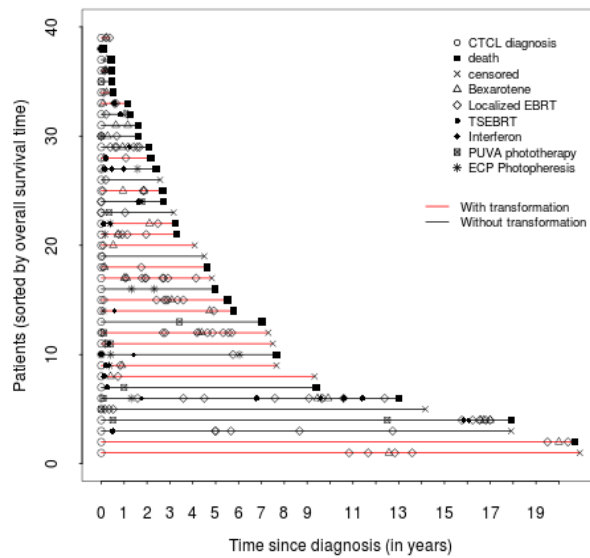

Figure 2. A diffuse dermal infiltrate of uniform population of atypical lymphocytes is present. Note the epidermis is ulcerated (2x).
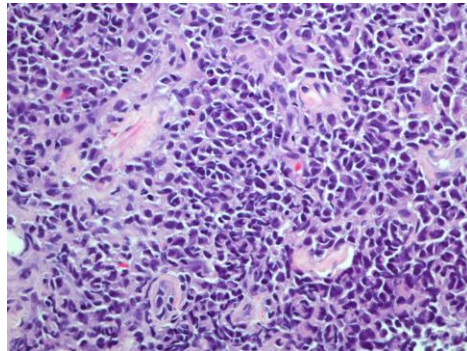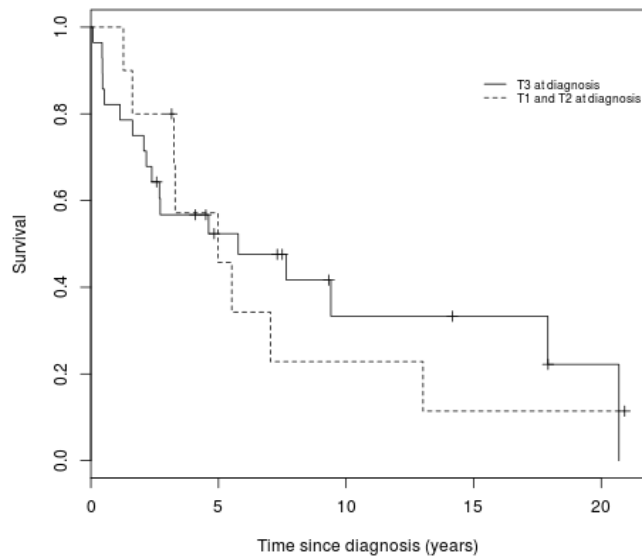

**Figure 3.** High power view of atypical lymphocytes (40x).
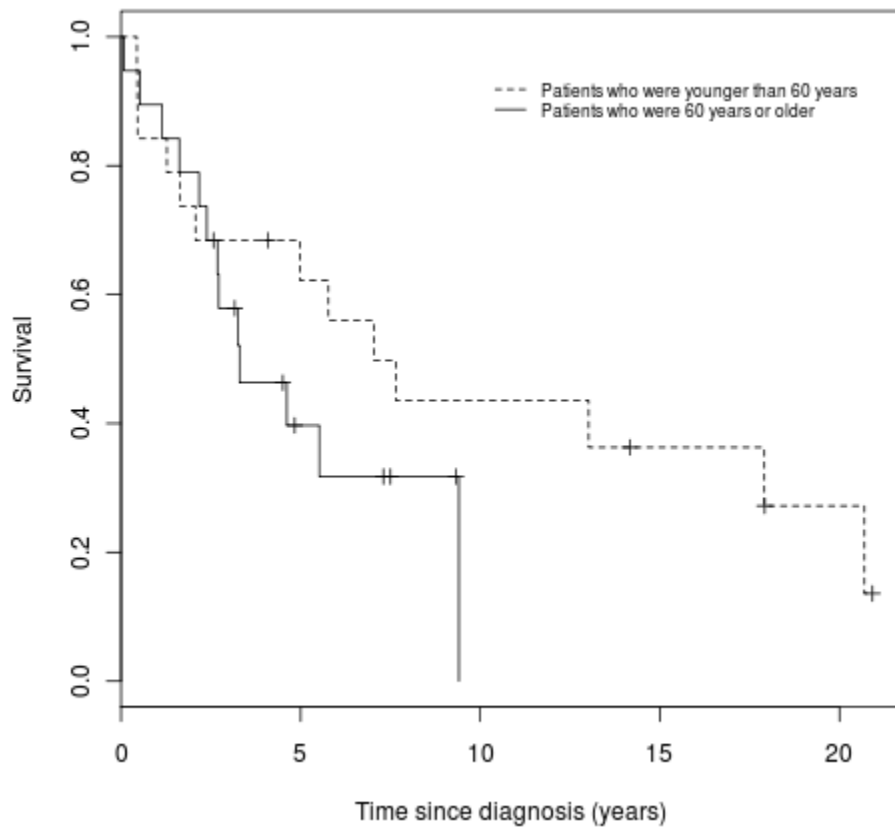
Figure 4: Tumor Stage Mycosis Fungoides. Overall survival for patients who were 60 years older vs. younger at diagnosis.

Figure 5: Tumor Stage Mycosis Fungoides. Timelines of treatment interventions

Figure 6: Tumor Stage Mycosis Fungoides. Overall survival for patients who had T3 stage (tumor) vs. T1 and T2 stages (patches/plaques) at diagnosis
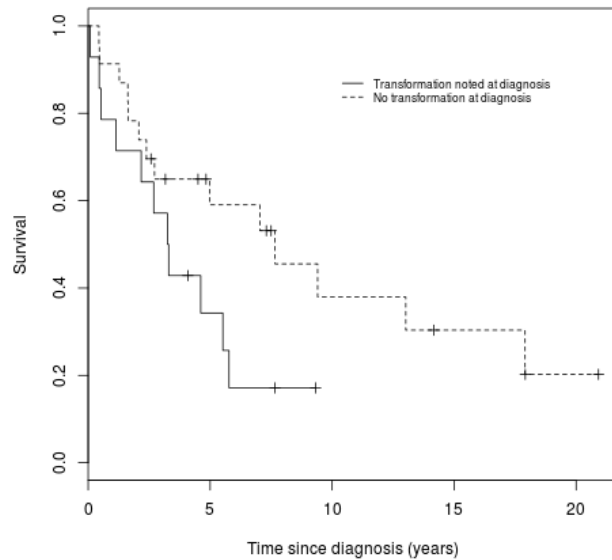
Figure 7: Tumor Stage Mycosis Fungoides. Overall survival for patients with tumor stage MF with and without transformation at diagnosis.

Among the patients who were younger than 60 years at the time of their first diagnosis (n = 19), median OS was 7.0 years (95% CI: 2.1-17.9), compared with 3.3 years (95% CI: 2.4-9.3) in patients who were 60 years of age or older at initial diagnosis (p = 0.196) (Figure 4).

Treatment event chart for patient cohort:

A timeline of treatment interventions for each patient is depicted in Figure 5. The median number of treatments that each patient received was five (Range: 1-25). Fifteen patients (38%) had transformation at time of diagnosis while five patients (13%) had transformation during disease course. The number of patients that received the following treatments included: bexarotene (26), localized electron beam radiation therapy (LEBRT) (32), chemotherapy (7), total skin electron beam radiation therapy (TSEBRT) (13), ECP (10), phototherapy with psoralen plus ultraviolet A (PUVA) (11), and interferon (11).

Durable responses (partial and complete) for all treatments:

The number of durable responses was 14 (54%; 11 PR, 3 CR) for bexarotene, 26 (81%; 3 PR, 23 PR) for LEBRT, 6 (86%; 5 PR, 1 CR) for chemotherapies, 8 (62%; 6 PR, 2 CR) for TSEBRT, 7 (70%; 5 PR, 2 CR) for ECP, 4 (36%; 3 PR, 1 CR) for PUVA, and 4 (36%; 3 PR, 1 CR) for interferon. If a patient had multiple trials of each therapy, only the first trial was analyzed to generate the

number of durable responses. All patients on bexarotene had a durable response to the treatment at some point in the course of treatment when taking into account all therapeutic trials

Treatment failures for all treatments:

The number of treatment failures from any cause: bexarotene (20/26), LEBRT (5/32), chemotherapy (4/7), TSEBRT (9/13), ECP (6/10), PUVA (4/11), and interferon (9/11). The median TTF for the following treatments was 7.5 months (95% CI: 3.1-12.4) for bexarotene and 2.2 months (95% CI: 1.0-3.0) for TSEBRT. If a patient had multiple trials of each therapy, only the first trial was analyzed to generate the number of treatment failures.

Overall survival:

The median survival time for the patient cohort was 5.5 years (95% CI: 2.7-17.9). The median survival time for patients with T1/T2 stage at diagnosis was 5 years (95% CI 3.2-7.0). The median survival time for patients with T3 stage at diagnosis was 5.8 years (95% CI 2.4-14.2) (Figure 6).

Comparison between bexarotene and non-bexarotene groups:

Twenty-six patients (67%) received oral bexarotene, whereas 13 (33%) did not. Patients in the bexarotene group were older (median age 61 years versus 56 years). Patients on bexarotene were more likely to have LCT at diagnosis and prior to initiation of bexarotene (56% vs. 8%).

Comparison between patients with tumor stage MF with or without transformation at first presentation:

In our study, 15/38 patients had LCT at time of presentation and 23/38 patients were without LCT at first presentation. Median OS for patients with LCT and without LCT was 3.3 (95% CI: 1.1-4.6) and 7.7 (95% CI: 2.7-14.2) years, respectively (p = 0.079) (**Figure 7**).

Discussion

Tumor stage (stage IIB) MF patients are identified by nodules and tumors on the skin that generally portend a worse prognosis than early patch/plaque stage MF. These patients typically have some degree of patch/plaque MF before appearance of tumors. The median interval between onset of symptoms and diagnosis of MF in our cohort was 3 years (IQR 0.7-10.0). As expected, several studies, including a recent study that included a cohort of 1502 patients with MF/Sezary Syndrome (SS), showed that more advanced stage was associated with reduced OS [6, 7, 10, 12]. This study validated the recently proposed International Society for Cutaneous Lymphomas (ISCL)/European Organisation for Research and Treatment of Cancer (EORTC) revised staging proposal [7]. Our group of tumor stage patients had a median survival of 5.5 years, which is consistent with current literature. For example, a retrospective study of patients with stage IIB (167 patients), IIIA (100 patients), or IIIB (56 patients) MF treated at a single institution reported median survival rates of 4.7, 4.7, and 3.4 years, respectively [7]. Most recently, a prospective study by Talpur et al. of patients with tumors (stage T3) treated at a single center reported a median survival rate of 5.96 years [13].

Our descriptive study identified potential prognostic markers on OS. Patient age at initial diagnosis of MF has been found to be predictive of OS [14]. Our data reflected this trend, with patients younger than 60 at the time of diagnosis having median survival of 7.0 years (95% CI: 2.1-17.9), compared with 3.3 years (95% CI: 2.4-9.3) in patients who were older than 60 at initial diagnosis, though this difference did not reach statistical significance, likely secondary to our small sample size (p value= 0.196). It has been hypothesized that with increasing age, patients experience poorer tolerance of therapies and weaker immune surveillance [14]. Interestingly, our data did not show that patients diagnosed with T1/T2 stage who progressed to develop tumors had significantly different survival compared to patients diagnosed with T3 tumors stage MF **(Figure 6).** Ten patients with T1/T2 stage at diagnosis had median survival of 5.0 years (95% CI 3.2-7.0). Twenty-eight patients with T3 stage at diagnosis had median survival of 5.8 years (95% CI 2.4-14.2). No direct comparisons were made from this data between the two groups, although it would be interesting to further determine why this cohort of patch/plaque stage patients who then progressed to develop tumors have no survival difference compared to the tumor stage at diagnosis patients. The lack of difference may also be attributed to the small sample size.

Apart from age and clinical stage, large cell transformation (LCT) in MF has been thought to be associated with an aggressive clinical course and a poor survival [6, 10, 12, 15]. LCT occurs more commonly in advanced-stage disease than early-stage disease and is especially common in tumor stage MF [16]. LCT was present in 55% of patients with tumor stage disease in a

study by Vonderheid, et al [17]. Most studies report a median survival that varies between 2 and 36 months [6]. In contrast, Agar et al. reported a median survival for patients with LCT of 8.3 years in a cohort of 70 patients with transformed MF at the time of first diagnosis [7]. Most recently, Benner et al. reported a median survival for stage IIB MF patients with LCT (25 patients) of 42 months compared to 53 months for patients without LCT (27 patients) at first presentation [6]. The differences in DSS and OS between both groups were not statistically significant (p value= 0.644 (DSS), 0.721(OS) [6]. The wide range in survival is possibly related to the small size of cohorts and heterogeneous patient population in the studies [6]. In our cohort, 15/38 (39.5%) patients had LCT at presentation. LCT appears to be a negative prognostic indicator given patients with median OS for patients with LCT and without LCT was 3.3 (95% CI: 1.1-4.6) and 7.7 (95% CI: 2.7-14.2) years, respectively (p value= 0.079) (Figure 7).

Treatment for tumor stage MF includes a variety of agents including skin directed therapies and systemic agents. Out of several treatment modalities analyzed, chemotherapies and LEBRT had the highest rate of durable response, 86% (6/7) and 81% (26/32), respectively. Patients receiving chemotherapy were likely also placed on subsequent treatment to prevent relapse, which may artificially increase the rate of durable response to chemotherapy.

In multinational studies by Duvic et al., bexarotene has been shown to be a safe and effective treatment for early-stage and refractory advanced-stage CTCL [18]. It has been used as both monotherapy and combination therapy for CTCL [19, 20]. In patients with refractory advanced-stage CTCL, phase II-III trial results in this multinational study reported bexarotene with response rates of 45 to 55 percent (10 to 20 percent complete) depending on the dosing of the systemic retinoid [18, 21, 22]. Our results were similar; patients on bexarotene had a 54% rate of durable response (14/26) based on first trial of treatment. However, a few patients on bexarotene had several therapeutic trials of this medication. When taking into account all therapeutic trials, all patients on bexarotene had a durable response to this treatment at one point during their course. Since treatment failure takes into account not only lack of response but also discontinuation of the medication secondary to side effects, cost, etc, the maximum therapeutic benefit of a modality may not have been realized on the first attempt of a medication. Patients on bexarotene did not have improved OS compared to patients who did not receive bexarotene. This may relate to a selection bias in treatment choice. Patients in the bexarotene group were older than those who did not receive the drug (mean of 61 versus 56 years). The patients in the bexarotene group were also more likely to have LCT (56% vs. 8%) upon diagnosis before treatment intervention. Older age and LCT are associated with decreased OS.

The chief limitation of this single-center study was its retrospective design, which may have introduced selection and referral biases. Another limiting factor to the data is that only the first therapeutic trial of each treatment was analyzed, even if a patient took the same treatment multiple times. This was done in order to hopefully minimize the overlap between therapeutic effects of different treatment regimens.

Conclusion

In conclusion, our study found patients with T1/T2 stage disease at diagnosis that progressed to develop tumors had no difference in survival compared to T3 stage at diagnosis patients. Further studies could aim to elucidate what separates these T1/T2 stage patients from other early patch or plaque stage MF patients such that they develop tumors and their survival is more consistent with tumor stage patients. Could there be differences in demographics, clinical characteristics, histopathology, or gene rearrangement profile? We also found that although older age at diagnosis and LCT were not statistically significant negative prognostic indicators, there seems to be a trend towards significance, which may have been achieved with a larger sample size and greater powered study. Larger prospective studies may help clarify how specific treatments impact disease course and survival.

References

1. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. Arch Dermatol. 2007 Jul;143(7):854-9. PubMed PMID: 17638728.
2. Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, Marcos-Gragera R, Maynadié M, Simonetti A, Lutz JM, Berrino F; HAEMACARE Working Group. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010 Nov 11;116(19):3724-34. doi: 10.1182/blood-2010-05-282632. Epub 2010 Jul 27. Erratum in: Blood. 2011 Mar 24;117(12):3477. PubMed PMID: 20664057.
3. Zackheim HS. Cutaneous T cell lymphoma: update of treatment. Dermatology. 1999;199(2):102-5. Review. PubMed PMID: 10559573.
4. van Doorn R, Zoutman WH, Dijkman R, de Menezes RX, Commandeur S, Mulder AA, van der Velden PA, Vermeer MH, Willemze R, Yan PS, Huang TH, Tensen CP. Epigenetic profiling of cutaneous T-cell lymphoma: promoter hypermethylation of multiple tumor suppressor genes including BCL7a, PTPRG, and p73. J Clin Oncol. 2005 Jun 10;23(17):3886-96. Epub 2005 May 16. PubMed PMID: 15897551.

5. Kim YH, Jensen RA, Watanabe GL, Varghese A, Hoppe RT. Clinical stage IA (limited patch and plaque) mycosis fungoides. A long-term outcome analysis. Arch Dermatol. 1996 Nov;132(11):1309-13. PubMed PMID: 8915308.
6. Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood. 2012 Feb 16;119(7):1643-9. doi: 10.1182/blood-2011-08-376319. Epub 2011 Dec 12. PubMed PMID: 22160616.
7. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, Robson A, Calonje E, Stefanato CM, Wain EM, Wilkins B, Fields PA, Dean A, Webb K, Scarisbrick J, Morris S, Whittaker SJ. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010 Nov 1;28(31):4730-9. doi: 10.1200/JCO.2009.27.7665. Epub 2010 Sep 20. PubMed PMID: 20855822.
8. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Jaffe ES, Harris NL, Stein H, Vardiman JW (Eds), IARC Press, Lyon 2001.
9. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, Zackheim H, Duvic M, Estrach T, Lamberg S, Wood G, Dummer R, Ranki A, Burg G, Heald P, Pittelkow M, Bernengo MG, Sterry W, Laroche L, Trautinger F, Whittaker S; ISCL/EORTC. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007 Sep 15;110(6):1713-22. Epub 2007 May 31. Review. Erratum in: Blood. 2008 May 1;111(9):4830. PubMed PMID: 17540844.
10. Salhany KE, Cousar JB, Greer JP, Casey TT, Fields JP, Collins RD. Transformation of cutaneous T cell lymphoma to large cell lymphoma. A clinicopathologic and immunologic study. Am J Pathol. 1988 Aug;132(2):265-77. PubMed PMID: 3261136; PubMed Central PMCID: PMC1880730.
11. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457.
12. Greer JP, Salhany KE, Cousar JB, Fields JP, King LE, Graber SE, Flexner JM, Stein RS, Collins RD. Clinical features associated with transformation of cerebriform T-cell lymphoma to a large cell process. Hematol Oncol. 1990 Jul-Aug;8(4):215-27. PubMed PMID: 2210690.
13. Talpur R, Singh L, Daulat S, Liu P, Seyfer S, Trynosky T, Wei W, Duvic M. Long-term outcomes of 1,263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. Clin Cancer Res. 2012 Sep 15;18(18):5051-60. doi: 10.1158/1078-0432.CCR-12-0604. Epub 2012 Jul 31. PubMed PMID: 22850569; PubMed Central PMCID: PMC3857608.
14. Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blewitt O, McCormack C. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood. 2008 Oct 15;112(8):3082-7. doi: 10.1182/blood-2008-05-154609. Epub 2008 Jul 22. PubMed PMID: 18647960.
15. Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Blood. 1998 Aug 15;92(4):1150-9. PubMed PMID: 9694702.
16. Cerroni L, Rieger E, Hödl S, Kerl H. Clinicopathologic and immunologic features associated with transformation of mycosis fungoides to large-cell lymphoma. Am J Surg Pathol. 1992 Jun;16(6):543-52. PubMed PMID: 1599034.
17. Vonderheid EC, Tam DW, Johnson WC, Van Scott EJ, Wallner PE. Prognostic significance of cytomorphology in the cutaneous T-cell lymphomas. Cancer. 1981 Jan 1;47(1):119-25. PubMed PMID: 6970070.
18. Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, Crowley C, Yocum RC; Bexarotene Worldwide Study Group. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol. 2001 May 1;19(9):2456-71. PubMed PMID: 11331325.
19. Talpur R, Ward S, Apisarnthanarax N, Breuer-Mcham J, Duvic M. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol. 2002 Nov;47(5):672-84. PubMed PMID: 12399758.
20. Singh F, Lebwohl MG. Cutaneous T-cell lymphoma treatment using bexarotene and PUVA: a case series. J Am Acad Dermatol. 2004 Oct;51(4):570-3. PubMed PMID: 15389192.
21. Abbott RA, Whittaker SJ, Morris SL, Russell-Jones R, Hung T, Bashir SJ, Scarisbrick JJ. Bexarotene therapy for mycosis fungoides and Sézary syndrome. Br J Dermatol. 2009 Jun;160(6):1299-307. doi: 10.1111/j.1365-2133.2009.09037.x. Epub 2009 Feb 16. PubMed PMID: 19222457.
22. Duvic M, Martin AG, Kim Y, Olsen E, Wood GS, Crowley CA, Yocum RC; Worldwide Bexarotene Study Group. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001 May;137(5):581-93. PubMed PMID: 11346336.