Disease characteristics, prognosis, and response to therapy in patients with large-cell transformed mycosis fungoides: A single-center retrospective study

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Background: Mycosis fungoides with large-cell transformation (MF-LCT) is associated with an aggressive clinical course, yet data comparing treatment outcomes in MF-LCT are sparse.

Objective: To compare treatment outcomes and to determine disease prevalence and characteristics associated with survival in MF-LCT.

Methods: A retrospective review was conducted of mycosis fungoides patients from 2012 to 2020 treated at Thomas Jefferson University. Patients with histopathologic diagnosis of MF-LCT were included. Treatment outcomes were assessed by mean changes in the modified Severity Weighted Assessment Tool (mSWAT) and stage.

Results: Of 171 patients with mycosis fungoides, 23 (13.4%) had histologic diagnosis of MF-LCT. The overall 5-year survival rate for MF-LCT was 74% and was not significantly associated with sex, age, or initial stage at the time of MF-LCT diagnosis. Brentuximab vedotin showed the greatest mean decrease in mSWAT (−20.53) and stage progression (change in Δ stage: −0.4) in MF-LCT compared to oral bexarotene (ΔmSWAT: +4.51; Δstage: +0.27), skin-directed therapy (ΔmSWAT: −5.93; Δstage: −0.08), and chemotherapy (ΔmSWAT: +4.97; Δstage: +0.85).

Limitations: Single-center retrospective design, and patients often on multiple treatment modalities.

Conclusions: We report superior treatment outcomes for brentuximab vedotin compared to oral bexarotene, skin-directed therapy, and chemotherapy in MF-LCT in both early and advanced disease. (J Am Acad Dermatol 2022;86:1285-92.)

Key words: brentuximab vedotin; cutaneous T-cell lymphoma; large-cell transformation; mycosis fungoides.

INTRODUCTION

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL), characterized by a proliferation of small- to medium-size atypical, usually $CD4^+$ T cells in the skin.[1] Generally, MF has an indolent disease course when diagnosed at the patch or plaque stage[2] but can progress to form skin tumors or involve blood, lymph nodes, or

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viscera.[1,3,4] MF with large-cell transformation (MF-LCT) is an aggressive subtype defined by the presence of large cells (>4 times the size of a small lymphocyte) comprising greater than 25% of the lesion infiltrate or the presence of microscopic nodules of large cells.[5] The prevalence of MF-LCT varies widely and was reported in 3% to 34% of MF cases from 1987-2019.[1,2,4-19] Similarly, reported mortality rates vary and range from 8% to 69% in the literature (Supplemental Table 1; available via Mendeley at https://data.mendeley.com/datasets/vjww3fsk65/1).[1,2,4-19]

While MF-LCT is associated with a more-aggressive disease course,[5,6,8] objective data on efficacy of various treatment options in MF-LCT are lacking. This partly stems from excluding patients with MF-LCT from most past or ongoing MF clinical trials.[20] Furthermore, few studies that evaluated treatment outcomes in MF-LCT lacked data on patients with early-stage disease. A recent study of chemotherapeutic agent treatment outcomes in MF-LCT assessed patients only with advanced stage disease and lacked parallel treatment arms.[21] A subanalysis of the ALCANZA trial (brentuximab vedotin versus methotrexate or bexarotene in $CD30^+$ CTCL) included primarily MF-LCT patients with advanced stage disease.[22,23]

In this study, we compare the outcomes of 4 different treatment regimens in patients with MF-LCT of both early and advanced stage. Here, we present data obtained from a single-center multidisciplinary cutaneous lymphoma clinic and provide a review of prevalence, survival characteristics, and treatment outcomes in our MF-LCT cohort.

CAPSULE SUMMARY

- Data comparing treatment efficacies in large-cell transformed mycosis fungoides are limited.
- Patients on brentuximab vedotin therapy had superior outcomes in large-cell transformed mycosis fungoides compared to those on oral bexarotene, skin-directed therapy, and chemotherapy, with the greatest reduction in overall modified Severity Weighted Assessment Tool and lymph node response.

METHODS

Approval was obtained from the Institutional Review Board at Thomas Jefferson University. The cutaneous lymphoma database at Thomas Jefferson University was retrospectively reviewed for the period between 2012 and 2020. Clinical history, histopathologic data, and immunohistochemical studies were reviewed. All patients with a confirmed diagnosis of MF were identified. Within this group, patients with a histopathologic diagnosis of MF-LCT in at least 1 skin biopsy who continued to exhibit large-cell transformation in all subsequent biopsies since the original MF-LCT diagnosis were included in the study. A diagnosis of LCT was confirmed using the definition by Salhany et al[5] for the presence of large cells that are more than 4 times the size of a small lymphocyte and that comprise more than 25% of the lesion infiltrate. After the original diagnosis had been made (JS), a secondary blinded histopathology review of all patient biopsies in this study was conducted by a dermatopathologist (JC) to confirm MF-LCT on histopathology.

In order to compare response to different therapies, 4 treatment categories were created: (1) brentuximab vedotin, (2) oral bexarotene, (3) skin-directed therapy (topical steroids, tacrolimus, mechlorethamine, narrowband ultraviolet B, psoralen and ultraviolet A, local radiation, total skin electron beam therapy), and (4) chemotherapy (romidepsin, vorinostat, praltrexate, ICE [ifosfamide, carboplatin, etoposide], and CHOP [cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone]). For simplicity, histone deacetylase inhibitors were grouped with chemotherapies.

Patients with MF-LCT are often placed on multiple therapies. To accurately place patients in appropriate treatment groups, a map demonstrating type and duration of treatment was designed for each subject. An example of this map is illustrated in Supplemental Figure 1. Based on treatment maps, each patient was placed in 1 or more treatment categories for the periods of time undergoing nonoverlapping treatments. For example, the patient depicted in Supplemental Figure 1 was placed in 3 different, nonoverlapping treatment groups and assessed separately for response to each treatment during its respective time period. Aside from concomitant topical steroid use, data from any overlapping therapy groups were omitted.

At each visit, body surface area, modified Severity Weighted Assessment Tool (mSWAT), and tumor-node-metastasis-blood staging data were collected. Staging information and mSWAT at the initiation and at the end of a treatment were recorded (Supplemental Fig 1). Changes in mSWAT from the beginning to the end of each treatment period for an individual patient were assessed and used to calculate the overall mean mSWAT change for each treatment category.

Changes in lymph node, blood, and visceral involvement were assessed using Olsen's response

Abbreviations used:

CR:	complete response
CTCL:	cutaneous T-cell lymphoma
MF:	mycosis fungoides
MF-LCT:	mycosis fungoides with large-cell transformation
mSWAT:	modified Severity Weighted Assessment Tool
PD:	progressive disease
SD:	stable disease
SDT:	skin-directed therapy

criteria.[24] We devised a point-value rating system to simplify and numerically quantify overall disease and stage progression. We used this scoring system as an additional tool, beyond mSWATs and organ-based response criteria, to quantify the cumulative state of disease for each treatment category. Progression from early-stage disease (IA, IB, IIA) to IIB was assigned +1 point; stage IIB to stage IIIA/IIIB was assigned +1 point; stage IIIA/IIIB to stage IVA was assigned +1 point; stage IVA to stage IVB was assigned +1 point; remission to early-stage was assigned +1 point; and any stage to death was assigned +1 point (Supplemental Fig 1). Conversely, each regression in stage was given a negative point-value score.

Using this point-value system, the highest theoretical score for stage progression is +6, corresponding to a patient in remission progressing to stage IVB and ultimately death when on a given treatment. Conversely, the best score for stage changes is −5, corresponding to a patient formerly in stage IVB who achieves remission. Changes in stage from beginning to end of each treatment period for an individual patient were assessed and used to calculate the overall change in stage for each treatment category.

Fisher's exact test was used to compare demographic and clinical-histological characteristics between living and deceased MF-LCT patients. Survival curves were generated using a Kaplan-Meier estimator.

RESULTS

Of 171 patients diagnosed with MF in Thomas Jefferson University's cutaneous lymphoma database, 23 were confirmed by our in-house dermatopathologist to have 1 or more biopsies showing MF-LCT, giving a prevalence of 13.4%. Within the first 2 years of MF diagnosis, 91.3% (n = 21) of patients underwent LCT. The median time interval from MF diagnosis to MF-LCT diagnosis was 16 months. LCT was present at the time of MF diagnosis in 43.4% (n = 10) patients. During the 8-year time frame of this retrospective study, 5 patients with MF-LCT died of disease and 1 died of an unrelated cause. Additionally, 4 of the 5 patients who died from disease passed away while on chemotherapy. Overall survival from the time of MF-LCT diagnosis ranged from 11 to 56 months and median survival was 22 months, with the overall 5-year survival rate of 74% (Fig 1, *A*). Patients diagnosed with LCT at early-stage disease had a 60.95% 5-year survival rate while those diagnosed at late-stage disease had an 82.50% 5-year survival rate (P = .558) (Fig 1, *B*).

Most patients were diagnosed with MF-LCT after 60 years of age (65.2%, n = 15), including those who died during the study period (83%, n = 5) (Fig 1, *C*). The median age at the time of LCT diagnosis of living patients was 64.0 years (range, 34-83 years) and 69.5 years (range, 56-82 years) for deceased patients. Most of our MF-LCT patients were male (70%, n = 16), in both living (65%, n = 11) and deceased (83%, n = 5) cohorts (Fig 1, *C*).

The overall MF-LCT patient population was almost equally divided between African American and White patients: 43.5% (n = 10) were African American; 43.5% (n = 10) were White; 8.7% (n = 2) were Hispanic; and 4.3% (n = 1) were Asian. Of deceased patients, 50% (n = 3) were African American and 50% (n = 3) were White (Fig 1, *C*).

When assessing stage at the time of MF-LCT diagnosis, early and advanced stages were almost equally represented in our cohort. Overall, 43.4% (n = 10) were at an early stage at the time of MF-LCT diagnosis and 50% (n = 3) of deceased patients were at an early stage at the time of diagnosis (Fig 1, *C*).

Pathologic characteristics showed 96% (n = 22) of overall and 100% (n = 6) of deceased patients with $CD30^+$ (Fig 1, *C*). Additionally, 65% (n = 15) of all MF-LCT patients exhibited syringotropism; 48% (n = 11) exhibited epidermotropism; and 35% (n = 8) exhibited folliculotropism. Thirty-nine percent (n = 9) of patients had an elevated serum lactate dehydrogenase of > 220 U/L within 2 weeks of MF-LCT diagnosis. With respect to the above characteristics, including age (P = .369), sex (P = .621), race (P = 1), stage at transformation (P = 1), $CD30^+$ (P = 1), and other histopathologic criteria, we did not detect statistically significant differences between living and deceased MF-LCT cohorts (Fig 1, *C*).

Changes in mSWATs were calculated for patients of all stages in each treatment group and displayed in a waterfall plot (Fig 2, *A*). Mean changes in mSWAT were calculated for each treatment group for all stages (Fig 2, *B*), early stage (Fig 2, *C*), and late stage (Fig 2, *D*). Brentuximab vedotin showed the greatest improvement in mSWAT, with a mean mSWAT

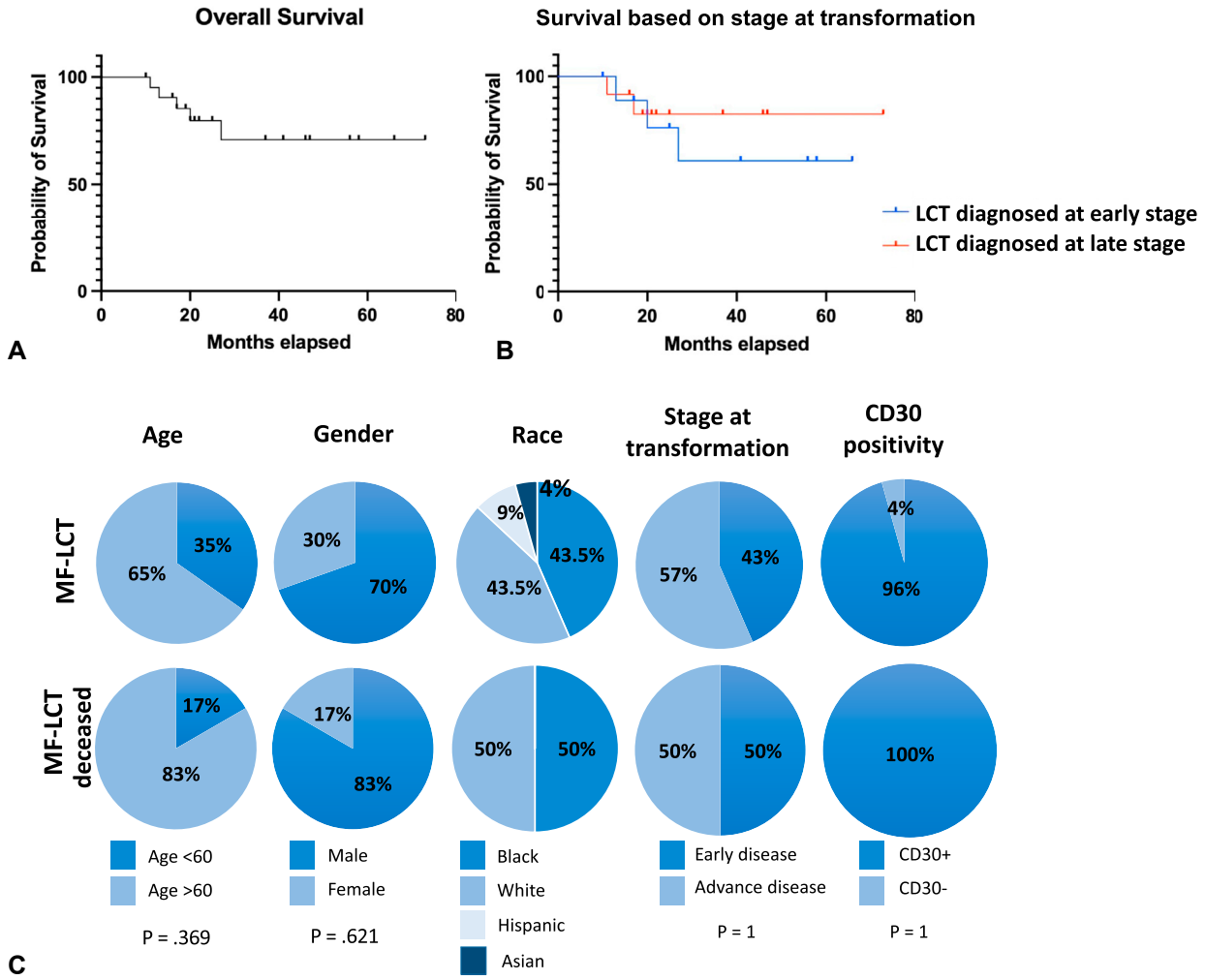


Fig 1. Patient survival, demographics, and histologic characteristics. *Top left,* Kaplan-Meier survival curve for Thomas Jefferson University's 23 patients after MF-LCT diagnosis. *Top right,* Comparison of Kaplan-Meier survival curves of patients diagnosed during early (IA-IIA) versus late stage (IIB+) with MF-LCT. *Bottom,* Comparison of age, sex, race, stage at transformation, $CD30^+$ between overall MF-LCT patients (*top*) and deceased patients (*bottom*). The *P* values for each category are calculated to compare living patients with deceased patients. *MF-LCT,* Mycosis fungoides with large-cell transformation; *LCT,* large-cell transformation.

change of −20.53 (all stages), −6.2 (early stage), and −33.75 (late stage). The mean change of mSWAT for oral bexarotene was a progression of +4.51 (all stages), improvement of −4.92 (early-stage), and progression of +19.92 (late stage). The skin-directed therapy (SDT) group demonstrated a mean mSWAT improvement of −5.39 (all stages), progression of +5.63 (early stage), and improvement of −12.73 (late stage). Chemotherapy patients were all late stage and progressed with a mean mSWAT change of +4.97. It should be noted that of the patients who received chemotherapy, 5 received prior treatment with brentuximab vedotin, 3 received oral bexarotene, and 5 received SDT.

Using Olsen's response criteria, involvement of lymph nodes, blood, and viscera were assessed in each patient (Fig 3, *A*). More patients in the brentuximab vedotin treatment group achieved a complete response (CR) for lymph node involvement compared to oral bexarotene, SDT, or chemotherapy groups. Four patients who received brentuximab vedotin therapy had lymph node involvement; 2 achieved CR, 1 remained at stable disease (SD), and 1 had progressive disease (PD). Conversely, there were more patients in the chemotherapy group, with SD and/or PD for lymph node involvement. Four patients remained at SD and 1 patient had PD while on

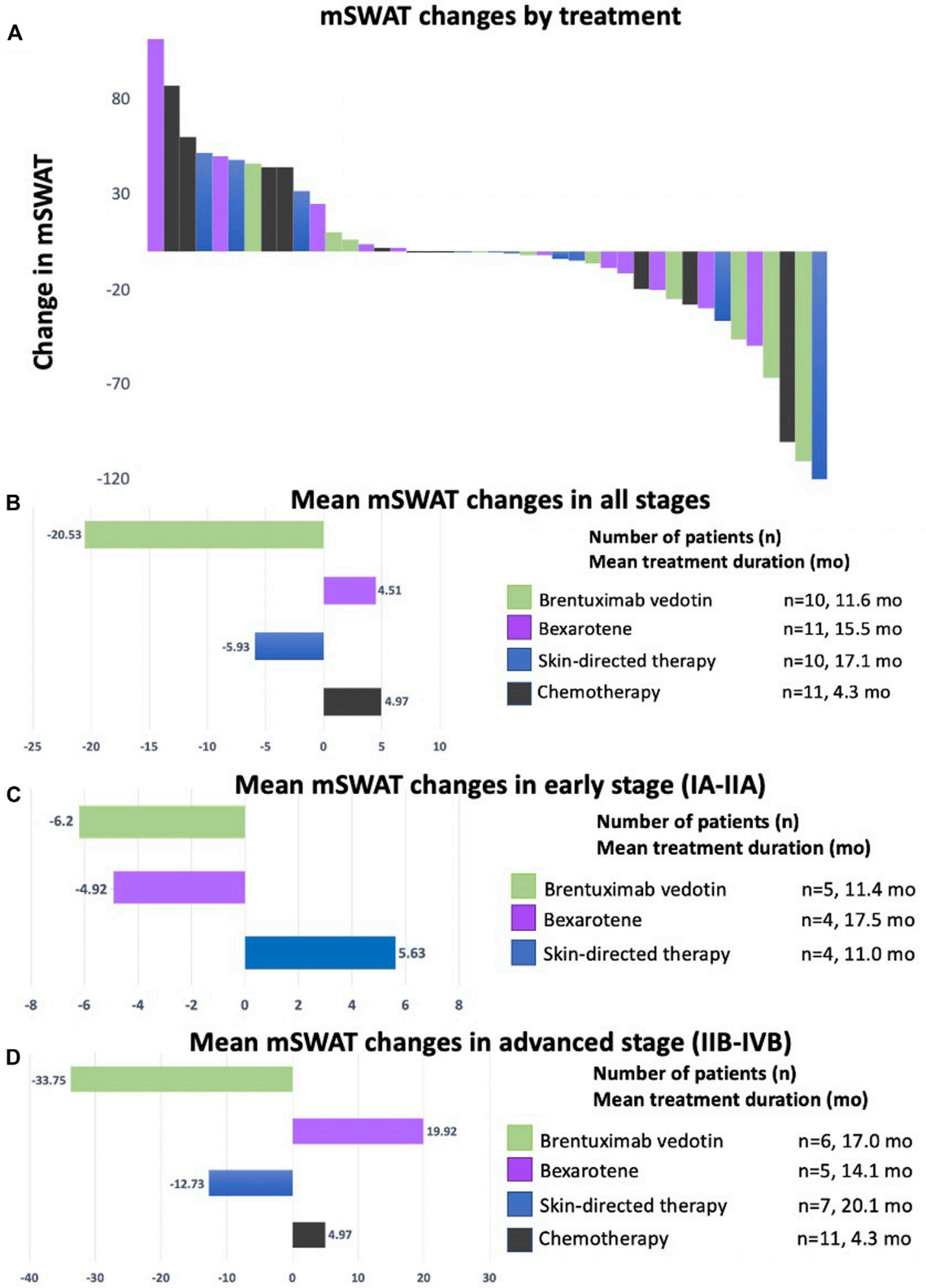
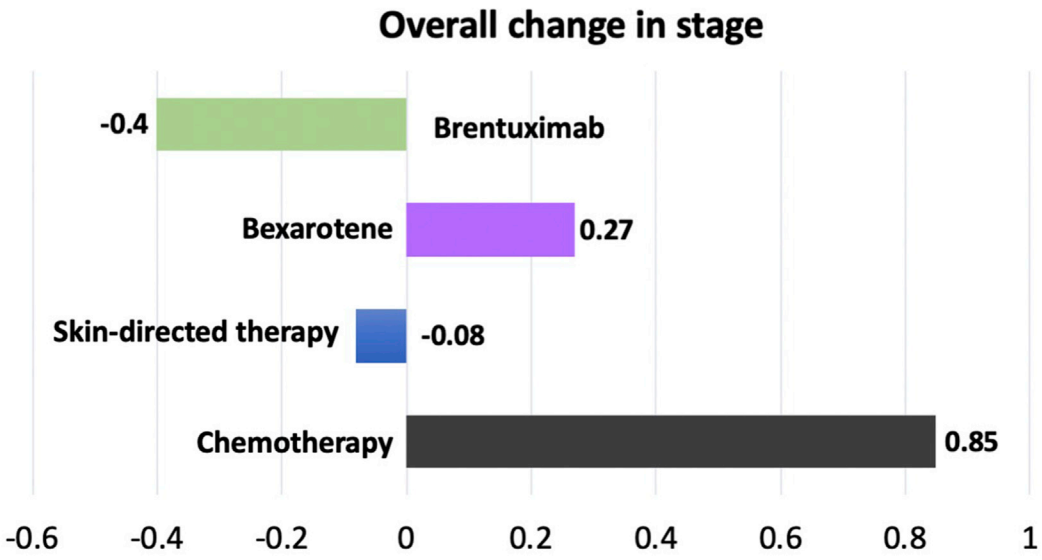


Fig 2. Changes in mSWATs based on treatment. **A,** Forty-two patient entries were included in the waterfall plot analysis and arranged in order from the greatest increase in mSWAT to the greatest decrease in mSWAT. **B,** Mean of overall change in mSWAT was calculated for each treatment group. **C,** Mean of overall change in mSWAT in those with early-stage mycosis fungoides with large-cell transformation was calculated for each treatment group. **D,** Mean of overall change in mSWAT in those with advanced stage mycosis fungoides with large-cell transformation was calculated for each treatment group. *mSWAT,* Modified Severity Weighted Assessment Tool.

	Brentuximab Vedotin	Bexarotene	Skin-directed Therapy	Chemotherapy
Response in Lymph Nodes				
No nodal involvement/unknown	60% (6)	100% (11)	75% (9)	38% (5)
Complete Response (CR)	**20%(2)**	0	0	8%(1)
Partial Response (PR)	0	0	0	0
Stable Disease (SD)	10%(1)	0	0	**31%(4)**
Progressive Disease (PD)	10%(1)	0	8% (1)	**8%(1)**
Response in Blood				
No blood involvement/unknown	100% (10)	100% (10)	83% (10)	70% (9)
Complete Response (CR)	0	0	0	0
Partial Response (PR)	0	0	0	0
Stable Disease (SD)	0	0	0	**8%(1)**
Progressive Disease (PD)	0	0	8% (1)	**15%(2)**
Response in Viscera				
No visceral involvement/unknown	90% (9)	100% (11)	100% (11)	77% (10)
Complete Response (CR)	0	0	0	0
Partial Response (PR)	0	0	0	0
Stable Disease (SD)	10%(1)	0	0	15%(2)
Progressive Disease (PD)	0	0	0	0

A



B

Fig 3. Patient response in lymph nodes, blood, and visceral involvement and overall change in stage. *Top,* Patient response in lymph nodes, blood, and visceral involvement using Olsen's response criteria. *Bottom,* Overall changes in stage using adapted point-value system for each treatment group.

chemotherapy. Only 1 patient achieved CR for lymph nodes on chemotherapy.

Similar findings for blood involvement were noted: more patients on chemotherapy had SD and/or PD compared to patients on brentuximab vedotin, oral bexarotene, or SDT. Of the 3 patients who had visceral involvement, 2 patients were on chemotherapy and 1 was on brentuximab vedotin.

All 3 patients maintained SD with visceral involvement.

Using the adapted point-value system, changes in stage were calculated for patients in each treatment group (Fig 3, *B*). Patients on brentuximab vedotin experienced the greatest improvement in stage change, with an average stage change of −0.4 over a mean duration of 11.6 months. SDT showed an average stage change of −0.08 over a mean duration of 17.1 months. Oral bexarotene had an average stage progression of +0.27 over a mean duration of 15.5 months. Chemotherapy showed an average stage progression of +0.85 over a mean duration of 4.3 months.

DISCUSSION

In this single-center retrospective review, we analyzed prevalence, survival rates, clinical and histologic factors associated with survival, and treatment outcomes in our cohort of 23 patients with MF-LCT. We found the prevalence (13.4%) and 5-year survival rates (74%) to be similar to previous studies (Supplemental Table 1), and we did not identify any histologic or demographic characteristics in our cohort that were significantly associated with poor survival.[1,2,4-19] Several characteristics have been associated previously with poor survival in MF-LCT, including: LCT diagnosis at <2 years after initial MF diagnosis,[1,8] advanced stage (IIB-IVB), >60 years of age at the time of large-cell transformation,[1,2,9,10,14] elevated serum lactate dehydrogenase levels,[1,2,14] $CD30^-$,[1,4,10,15] and folliculotropic histologic subtype.[4,14] None of the above characteristics were significantly associated with poor survival in our MF-LCT cohort.

Although it did not reach statistical significance, this data revealed a lower 5-year survival rate for patients diagnosed with MF-LCT in early stages compared to those diagnosed with MF-LCT in late stages. This finding underscores the necessity for prompt and more-intensive treatment and monitoring for patients who develop transformation in earlier stages. It should be noted that while this study found no statistically significant difference in the prevalence of folliculotropism between our deceased versus live MF-LCT cohorts, it was not able to distinguish fully the individual contribution of LCT versus folliculotropism to survival.

In this study, the median time interval from MF diagnosis to MF-LCT was 16 months. While this fits within the median time interval reported in the literature, it must be noted that this range varies considerably: from 10 months[4] to 6.5 years.[9] LCT was present at the time of MF diagnosis in 9 of our patients; however, all of these patients had exhibited symptoms for a significant time before diagnosis.

This study is unique in comparing treatment outcomes in a substantial cohort of MF-LCT patients diagnosed in early stages. In cohort, both early and advanced MF-LCT patients treated with brentuximab vedotin had the highest improvement in skin involvement measured by a decrease in mSWATs compared to those treated with oral bexarotene, SDT, or chemotherapy. More patients on brentuximab vedotin achieved a CR in lymph node involvement compared to all other treatment groups. In addition, based on a point-value system to quantify changes in stage, brentuximab vedotin showed the greatest regression in stage when compared to oral bexarotene, SDT, and chemotherapy.

Brentuximab vedotin is a CD30-binding antibody-drug conjugate that was approved by the Food and Drug Administration and European Medicines Agency in 2017 for use in $CD30^+$ CTCL.[2,17,18] A summary of clinical trials and case reports assessing brentuximab vedotin in the treatment of CTCL is depicted in Supplemental Table 2.[22,23,25-32] Only a few of these studies included MF-LCT patients, mainly of advanced stage disease or with no comparative treatment arms. This study featured nearly even proportions of early stage (43%) and advanced stage (57%) MF-LCT disease and included 3 comparative treatment arms for brentuximab vedotin. The results complement findings of Kim et al[27] and the ALCANZA[23] trial in suggesting brentuximab vedotin as a potential first-line agent for treatment of MF-LCT.[23,27]

Inherent limitations for this study are its retrospective and nonrandomized design and a small cohort size; however, most existing MF-LCT studies include samples smaller in size. In addition, because patients with MF-LCT often receive multiple treatment modalities and overlapping therapies, categorizing patients into treatment groups was a challenge. It is important to note that patients in the chemotherapy group comprised a more recalcitrant subpopulation who received multiple prior treatments. As a result of the study's retrospective design, it was not possible to control whether patients with the same initial disease characteristics were placed in various treatment groups when determining relative efficacy. Finally, additional biopsies to confirm MF-LCT over time were not necessarily obtained at each treatment transition point.

Conflicts of interest

None disclosed.

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