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Outcomes of Patients with Transformed Mycosis Fungoides: Analysis from a Prospective Multicenter US Cohort Study

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Abstract

INTRODUCTION: We examined patient characteristics, treatments and outcomes of transformed mycosis fungoides (tMF) patients from COMPLETE: a large, multicenter, prospective cohort study of peripheral T-cell lymphoma patients in the US.

METHODS: Patients with tMF were enrolled in COMPLETE at the time of transformation. For this analysis, we identified tMF patients with completed baseline, treatment and follow-up records. Median survival was assessed using Kaplan-Meier methodology.

RESULTS: Of the 499 patients enrolled in COMPLETE, 17 had tMF. Median age was 61; 53% were male, 9 had elevated lactate dehydrogenase (LDH) and 9 had lymph node involvement. About one-quarter of the patients were African American and 47% had CD30+ disease. Median time to transformation was 53 months. All patients received systemic therapy, with 19% receiving concomitant radiotherapy. Most patients (87%) received single agents, including liposomal doxorubicin, pralatrexate and gemcitabine. Eight patients (50%) had reported responses to therapy. Median survival was 18 months. One- and two-year survival rates were 56% and 44%, respectively.

CONCLUSIONS: tMF often express CD30 and present with lymph-node involvement. Responses have been seen with single agents, but survival remains poor. Novel treatment approaches are urgently needed to improve outcomes.

MicroAbstract:

Transformed mycosis fungoides (tMF) is a rare variant of MF with an aggressive course. In this study, we describe the patient characteristics, treatments and outcomes of 17 tMF patients in COMPLETE: a multicenter, prospective US cohort study of peripheral T-cell lymphoma. Responses were observed with single agents, but survival remains poor. Novel treatment approaches are urgently needed to improve outcomes.

INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin lymphomas characterized by skin infiltration of neoplastic T-lymphocytes. Mycosis fungoides (MF), an epidermotropic type of primary CTCL, is characterized by infiltrates of small to medium T-cells with cerebriform nuclei.¹ The clinical course of MF is generally indolent over several years, with slow progression from patches to plaques and eventually the development of cutaneous tumors, or erythroderma involving lymph nodes and extranodal sites.^{2,3} Overall, MF has been shown to have a 5-year disease-specific survival of 88%, however survival declines substantially for different variants and in higher stages of MF.^{4, 5}

Transformed MF (tMF) typically occurs in 8%–23% of patients in the advanced tumor stage of the disease and is associated with the histologic appearance of large, atypical cells, which can be CD30- or CD30+.⁶ tMF is defined as the appearance of large atypical cells on the skin or in nodes that exceed 25% of infiltrating atypical T-cells or clusters of large cells with nuclei that are > 4 times the normal size.^{7, 8} Transformation of MF is associated with a more rapidly progressive, aggressive disease course and poor median survival, ranging from 1 to 4 years from the time of transformation, despite the use of aggressive chemotherapy.^{9–12}

The predictive factors associated with patient survival in tMF are unclear and have included CD30 expression, lactate dehydrogenase (LDH), sites of disease, and time of transformation after onset of MF.⁴ Early transformation of MF, within two years, older age (> 60 years), and extracutaneous invasion have been identified as important prognostic factors, and advanced stage of MF at the time of transformation and folliculotropism have been suggested as key factors related to patient survival.^{6, 9} Although CD30 expression has been found to be more common in advanced MF, studies have described it as a favorable prognostic factor in transformed MF.^{8, 10, 13}

Current treatment includes radiotherapy for localized disease and systemic agents for more disseminated disease. There is a lack of prospective treatment data in the medical literature related to tMF, with most data coming from retrospective analyses of institutional experiences or interventional trials. The objective of the current study was to prospectively examine the real-world outcomes for tMF patients treated in both academic and community settings.

PATIENTS AND METHODS

Study Eligibility

We analyzed data from the COMPLETE registry, a prospective multicenter cohort study of the demographics, treatment, and outcomes for patients with aggressive peripheral T-cell lymphomas from 56 centers representing both academic and community sites within the United States (NCT01110733).¹⁴

Patients with transformed MF were enrolled in COMPLETE at the time of identification of large cell transformation. All patients were identified based on local pathology reports and confirmation of the diagnosis by the treating physician. Seventeen of the 24 patients with tMF had pathology reviewed by a hematopathologist. The site of transformation was lymph node in 6 patients and skin in 18. After providing written informed consent, patients were followed prospectively for subsequent treatment(s) and outcomes. Patients were enrolled from practices that were self-designated as community or academic. Concomitant participation in clinical trials was permitted. Patients were followed longitudinally, and all demographic, treatment, and outcome data were recorded in the database. The treating investigator used the 2007 Response Criteria for Malignant Lymphoma to determine responses.¹⁵

Statistical Analysis

For this analysis, we identified tMF patients with completed baseline, treatment and follow-up records. Descriptive statistics were used to summarize the baseline characteristics of the study cohorts. For categorical and ordinal variables, frequencies and percentages were calculated. For continuous variables, descriptive statistics (number of patients, mean, median, standard deviation and range) were provided. Null hypothesis testing utilized chi-square, t-test and other non-parametric tests as required, with a two-tailed p value of 0.05 to reject the null hypothesis. Survival-based analyses were performed using Kaplan-Meier methodology with right censoring as appropriate and evaluated using a log rank test with a two-tailed p value of 0.05 to reject the null hypothesis. For all time-to-event analyses, date of informed consent was used as time zero. All analyses were performed using R version 3.1.0 or greater (The R Foundation for Statistical Computing - <https://www.r-project.org/>).

Cohort Selection

The dataset analyzed in this study was defined based on study entry criteria. Patients were included in the analysis if their initial treatment began within 30 days of enrollment/signed consent and treatment duration was four days or longer. The study allowed for patients with acute onset of disease requiring immediate therapy to be enrolled to not bias against patients with adverse factors. Patients were excluded from the dataset if they initiated front line therapy more than 30 days before or more than 30 days after signing informed. Baseline, initial treatment and follow-up records were required to be approved/locked by the principal investigator for a patient to be included in the analysis.

RESULTS

A total of 499 peripheral T-cell lymphoma patients were enrolled in COMPLETE between February 2010 and February 2014 from 41 academic- and 15 community-based practices. Of these, 24 patients were identified with a diagnosis of tMF; 17 of these had locked records available for this analysis. Patients were enrolled from six different centers, five academic and one community setting. Patients were eligible if they had a new diagnosis of tMF within 30 days of enrollment, as the intent of this prospective registry was to evaluate treatment and outcomes for patients at diagnosis. Patients may have had an antecedent history of MF for varying durations.

Characteristics of the 17 evaluable patients are shown in Table 1. The median age was 61 (range 57–71) and the median time from diagnosis of MF to diagnosis of transformation was 53 months (range 49–74). Sex distribution was equal between males and females, and 53% had elevated LDH. CD30 expression was recorded in 15 patients and was positive in 8 (53%), but the study did not quantitate the degree of CD30 positivity. Bone marrow was not obtained in all patients and visceral involvement was rare; reported in 5 of 24 patients (lung in 2, head and neck in 3) but only 1 of the 17 patients who had locked treatment records for this analysis; 53% had lymph node involvement by imaging studies.

Treatment modalities included local radiotherapy and systemic therapy in 19%, systemic therapy in 81%, and clinical trial in one patient. Anthracycline based therapy was used in 9 patients; 44% of patients had combination chemotherapy and 56% had a variety of single agents (Table 2). While 3 patients had intent to transplant, none were able to undergo stem cell transplantation due to progressive disease.

Response to initial therapy, included 2 complete responses and 6 partial responses (Table 3). Physician's Global Assessment was recorded as Marked Improvement in 4 patients, Mildly Improved in 1, Unchanged in 3, Mildly Worse in 3, Moderately Worse in 4, and Markedly Worse in 3. Following first line treatment, 13 patients were alive. The causes of death were treatment toxicity (n=1); disease progression (n=1); and other/not recorded (n=1). Physicians were asked to provide a global assessment of their patients after first line treatment, and they reported that 37% were improved, 13% were unchanged and 50% had worsened.

At a median follow-up of 2.7 years (range: 1.7 to 3.6 years), median overall survival was 18.4 months (95% CI: 5 months to not reached). (Figure 1) Median progression free survival was 8.4 months (95% CI: 2.6 to 43.2, Figure 1). A number of prognostic factors were examined and shown to have no influence on survival, including CD30 expression (P=0.83), LDH (P=0.92), and lymph node involvement (P=0.87). (Table 4)

DISCUSSION

While MF in its earliest stages is for most patients an indolent lymphoma, patients with tumor stage (T3) disease and tMF have a similar outcome with median survival of 19–36 months.^{8,9} The definition of LCT is based on the presence of >25% large cells or the presence of microscopic aggregates of large cells in the biopsy.^{6, 8, 13} A recent retrospective

review by Talpur et al. of 1900 MF patients reported an incidence of tMF of 9%.¹⁰ Patients with tMF at diagnosis had a worse outcome with a median survival of 3.6 years compared to those who developed tMF later (median survival 8.8 years). Talpur et al. reported that normal LDH and CD30 expression in > 10% of the tumor cells were favorable prognostic factors.¹⁰ The Cutaneous Lymphoma International Consortium Study of Outcomes reviewed 1275 patients with MF from around the world and found tMF in 215 patients (17%).⁴ The median survival in this group was 49 months (40–57 months), and in multivariate analysis of the whole cohort, they found that tMF, increased LDH, stage IV disease, and age >60 years were adverse prognostic features. The presence of LCT patches and plaques may have a different outcome than transformation noted in lymph nodes or cutaneous tumors.¹⁵

Events leading to large cell transformation and biologic features of tMF have not been well established. In one study, a differential expression of microRNAs was found when tMF was compared with folliculotropic MF, with overexpression of miR-181b and miR-326 in T-MF cases.¹⁶ In another study, 11 patients with tMF were examined by comparative genomic hybridization.¹⁷ Fifteen samples displayed unbalanced CGH profiles, with the most common abnormalities being gain of chromosome regions 1p36, 7, 9q34, 17q24-qter, 19, and loss of 2q36-qter, 9p21, and 17p. Five samples demonstrated gain of chromosome 17 and 7 cases had DNA ploidy ranging from hyperdiploid (2.78) to hypotetraploid (3.69) (mean 3.14+/-0.38). There were no consistent abnormalities among patients and thus no genetic signature for tMF. It is unclear whether any of these factors has prognostic significance.

There are few reports of treatment strategies and outcomes for tMF. Awar et al. showed that gemcitabine was effective in several patients.⁷ Pralatrexate, a novel folate analog, was shown to be active in a prospective clinical trial (PROPEL) in which tMF patients were enrolled.¹² Patients received pralatrexate at a dose of 30 mg/m² weekly x 6 weeks on a 7-week schedule. Of 12 enrolled patients, the objective response was 25% per independent central review and 58% per investigator assessment. The median duration of response and the median progression-free survival were 2.2 and 1.7 months, respectively by central review and 4.4 and 5.3 months, respectively, by investigator assessment. More recently, in a multicenter Phase II study of the CD30 targeting immunoconjugate Brentuximab Vedotin, 5 patients with tMF were enrolled and there was one complete and 2 partial responses.¹⁸ The ALCANZA Study randomized CD30+ patients with mycosis fungoides to brentuximab vedotin or investigator's choice (methotrexate or bexarotene) and reported a response rate of 56% for the brentuximab arm.¹⁹

In our series, most patients had a diagnosis of tMF years after the initial diagnosis of MF, so they were likely to have received other single agent therapies for their MF. That may have contributed to the investigator's treatment decision to use systemic therapy with an anthracycline containing regimen with either adriamycin or liposomal doxorubicin, a similar treatment strategy for aggressive T-cell lymphomas of other subtypes. Four patients did receive pralatrexate, and several other single agents with activity in MF were used. Even though half of these patients had CD30 expression, no patient received brentuximab vedotin since the drug was not available for MF at the time the study was accruing. The median duration of treatment was short (3 months) suggesting that treatment may have been ineffective, and of the three patients who had the intent to go to allogeneic transplant, none

were able to be transplanted. The median OS in this group was 14 months, which is shorter than what has been reported in retrospective reviews of patients who presented with tMF and those in whom transformation evolved, but this study reflects a real-world outcome for tMF patients identified at the time of transformation and using existing therapies dictated by physician's choice.

CONCLUSION

In summary, this prospective registry study of a small number of patients with tMF identifies that treatment patterns are largely focused on systemic multi-agent, anthracycline containing therapies, but these data pre-dated the approval of brentuximab vedotin. Outcomes remain poor for tMF and no patient in this series was able to undergo autologous/allogeneic transplantation. A prospective registry study is underway by the United States Cutaneous Lymphoma Consortium to evaluate the frequency of tMF and outcomes in the modern era with the availability of newer agents which are now in clinical trials.

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Clinical Practice Points:

- There is a lack of prospective treatment data in the medical literature related to tMF, with most data coming from retrospective analyses of institutional experiences or interventional trials.
- Large cell transformation in tMF can occur either in the skin or in lymph nodes or extracutaneous sites and often the large cells express CD30. Patients with transformation in skin patches or plaques have a better outcome than those with transformation in skin tumors or extracutaneous sites.
- The median time from diagnosis of MF to transformation varies but was 53 months in our Registry series.
- There are no clear treatment algorithms for tMF and patients are treated with combination chemotherapy regimens containing anthracyclines or single agent therapies. Most patients (87%) received single agents, including liposomal doxorubicin, pralatrexate and gemcitabine.
- Responses were seen with CHOP as well as with single agents, but survival remained poor with median survival of 18 months. Newer approaches are needed for these patients.

Figure 1A.
Overall Survival

Figure 1B.
Progression Free Survival

Table 1.**Characteristics of Transformed MF Patients (N=17)**

Characteristics at Time of Transformation	N	(%)
Median time to transformation (range), months *	53	(49–74)
Median age (range), years	61	(57–71)
Male sex	9	(53%)
Race	13	(76%)
White	4	(24%)
Black		
Elevated LDH	9	(53%)
CD30 expression	8	(47%)
Positive	7	(41%)
Negative	2	(12%)
Not assessed		
Lymph node involvement	9	(53%)
Bone marrow involvement	0	(0%)
Visceral disease	1	(6%)
ECOG 0–1	17	(100%)
International Prognostic Index (IPI)		
0–1 (Low Risk)	6	(35%)
2 (Low Intermediate)	3	(18%)
3 (High Intermediate)	6	(35%)
4–5 (High)	2	(12%)
Prognostic Index for PTCL (PIT)		
Group 1	3	(18%)
Group 2	7	(41%)
Group 3	7	(41%)

* Of 8 patients reported to have an original diagnosis of MF

PIT: remind the parameters

Table 2.

Transformed MF Patient Treatment (n=16)

First Treatment after Transformation	N	(%)
Treatment approach		
Local radiotherapy + systemic therapy	3	(19%)
Systemic therapy alone	13	(81%)
Transplant	0	(0%)
Transplant planned but not performed **	3	(19%)
Patient participating in a clinical trial for T-MF	1	(6%)
Systemic therapies ***		
Anthracyclines (liposomal doxorubicin/doxorubicin) ****	7 (1 CR, 2 PR)	(44%)
Pralatrexate	4	(25%)
CHOP/CHOP-like +/- etoposide	2 (1 SD)	(13%)
Bexarotene	2 (1 CR, 1 PR)	(13%)
Gemcitabine	2	(13%)
Romidepsin	2 (1 PR)	(13%)
Alisertib	1	(6%)
Dexamethasone	1	(6%)
Methotrexate	1 (1 PR)	(6%)
Vorinostat	1	(6%)
Median duration of treatment (range), months	3	(2–8)

Treatment information is missing for 1 patient. CR: complete response; PR: partial response

* Each patient may have up to 3 factors selected.

** Primary reason transplant not performed: progressive disease (n=2), other (n=1).

*** Sum may exceed 100% due to overlap in categories and combination use

**** 6 patients received an anthracycline outside of CHOP/CHOP-like regimen, most commonly Doxil alone

Table 3.

Response to First Line Treatment (N=16)

Overall Best Response	N	(%)
Complete Response	2	(13%)
Partial Response	6	(38%)
Stable Disease	1	(6%)
Progressive Disease	7	(44%)

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Table 4.

Predictors of Outcome (N=16)

Factors Predicting Survival	P value
CD30+	0.229
Lymph node involvement	0.546
International Prognostic Index (IPI)	0.542
Lactate dehydrogenase (LDH)	0.586
Gender	0.065 (favors Male sex)