RESEARCH ARTICLE

A retrospective comparative outcome analysis following systemic therapy in Mycosis fungoides and Sezary syndrome

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Cutaneous T-cell lymphomas (CTCL), with few exceptions, remain incurable and treatment is largely palliative. We performed a retrospective analysis of systemic treatment outcomes of patients diagnosed with MF/SS. We identified 223 patients with MF/SS evaluated at a single institution from 1997 to 2013. Disease stage at diagnosis, time of treatment, and treatments received were retrospectively analyzed using our CTCL database. The primary endpoint was time to next treatment (TTNT). Treatment outcomes were analyzed using Kaplan–Meier method and comparisons among groups were made using log-rank analysis. A superior TTNT was associated with retinoid or interferon therapies when compared with HDAC inhibitors or systemic chemotherapy. Retinoids and interferon were associated with superior TTNT in both limited-stage and advanced stage disease. Extracorporeal photophoresis (ECP) had a superior TTNT in Sezary Syndrome. HDAC inhibitors and chemotherapy were associated with inferior TTNT in both limited stage disease and advanced stage disease. With the exception of interferon, retinoids, or ECP, durable responses are rarely achieved with systemic therapies in MF/SS patients, particularly those with advanced-stage disease. Therefore, clinical trial participation with novel agents should be encouraged.
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■ Introduction

Primary cutaneous T-cell lymphomas (CTCL) are a heterogenous group of extranodal T-cell lymphomas involving the skin [1]. Cutaneous manifestations are variable, including patches/plaques, tumors, or diffuse erythroderma. Nodal, peripheral blood, or internal organ involvement is less common. The incidence rate of CTCL is around 10 per one million persons, with Mycosis fungoides (MF) and Sezary Syndrome (SS) comprising over half of all CTCL diagnoses [2].

Risk-stratification in MF/SS is largely based on TNMB staging, although other variables including gender, age, and folliculotropic disease also are prognostic and are included in the cutaneous lymphoma international prognostic index [3]. Patients with patches/plaques involving <10% of body surface area (stage IA) may anticipate an overall survival comparable to age matched controls. In contrast, overall survival in the setting of advanced-stage disease with visceral organ involvement is dismal, as responses to most currently available therapies are incomplete and rarely durable [4]. The risk of disease progression increases with increasing tumor (T) stage, with only 10% of patients with T1 disease undergoing progression to a higher T stage in comparison to approximately 80% in the setting of tumor stage (T3) disease [5]. Thus, the vast majority of patients with limited-stage disease (IA-IIA) may be conservatively managed with local skin-directed therapies (SDT). Progression to advanced-stage disease may be anticipated in approximately 24% of these patients [4]. Patients with advanced-stage disease (IIB-IV) may benefit from systemic treatments for disease control and symptom palliation. Unfortunately, treatment failure and eventual disease progression is common, highlighting the need for improved therapeutic strategies.

SDT, including topical steroids, PUVA, UVB, radiation and topical chemotherapies are used for localized disease control while systemic therapies are reserved for both limited-stage disease that is poorly controlled with SDT alone and advanced-stage disease. Systemic treatment options that have been utilized in MF/SS include retinoids [6], interferon alpha [7], single agent or combination chemotherapy [8–12], HDAC inhibitors [13], and antibody-based therapies [14,15]. For SS, extracorporeal photophoresis (ECP) is frequently used in the front-line setting [16]. In contrast to most alternative therapies, which are largely palliative, allogeneic stem cell transplantation is potentially curative [17,18]. Unfortunately, as MF/SS are rare lymphomas, few randomized clinical trials have been conducted and most of these trials involved patients with early stage disease [19]. Treatment guidelines are available but the evidence supporting these are largely based on data obtained from phase 2 clinical trials or retrospective studies [20–22].

Conventional chemotherapeutic agents, given alone or in combination, are generally not appropriate first-line options in MF/SS [23]. In MF, early aggressive therapy with radiation and multi agent chemotherapy does not improve disease-free or overall survival and is associated with considerable toxicity [24]. As the therapeutic armamentarium continues to expand, we sought to retrospectively compare outcomes among MF/SS patients treated with various systemic therapies.

Methods

Study population. We reviewed our CTCL database to identify pathologically confirmed MF and SS cases. CTCL cases identified by the University of Michigan cancer registry or those reviewed in a multidisciplinary CTCL tumor board are included in this retrospective database that includes patient and disease characteristics, including age, gender, TNMB stage, SDT and systemic treatments with date of initiation, time of treatment discontinuation and date of last follow up or date of death. In all, 223 cases pathologically confirmed MF and SS cases were identified between 1997 and 2013. Study approval was granted by the University of Michigan Institutional Review Board, in accordance with US federal regulations and Declaration of Helsinki.

Systemic treatment analysis. Systemic treatments were classified as chemotherapy, biological response modifiers (oral retinoids, interferon), HDAC inhibitors, denileukin diftitox, and ECP. The number of systemic treatments each patient underwent was counted to determine the line of treatment. SDT were not included when determining the line of therapy. In several instances, two therapies were initiated simultaneously: retinoid and denileukin diftitox, $n = 5$; retinoid plus interferon, $n = 3$; ECP plus HDAC inhibitor, $n = 3$; retinoid plus methotrexate, $n = 2$; retinoid plus ECP, $n = 1$. These cases were still included in their respective individual systemic treatment group. Treatments used in less than 10 patients (oral methotrexate, $n = 7$; brentuximab, $n = 6$) were not included in our analysis.

TABLE I. Patient Characteristics

	All	Limited stage	Extensive stage
Total number	223	178	45
Median age at diagnosis	59.9	59.2	63.7
Mycosis fungoides	210	177	33
Sezary syndrome	13	N/A	13
Number requiring systematic treatment	88(39.5%)	46(25.8%)	42(93.3%)
Average number of systematic treatments	2.6	2	3.2
3 year overall survival	86.2%	94.8%	54.8%

Data analysis. Time to next treatment (TTNT) was defined as the time from the date of treatment initiation to the time of initiation of the next systemic treatment or time of death, whichever occurred first. Initiation of a new SDT during a systemic treatment for local control was not regarded as a treatment failure, as long as the systemic treatment was continued during this time and a new systemic treatment was not initiated. However, the need for Total Skin Electron Beam therapy was considered as a systemic treatment failure. If treatment was discontinued due to disease progression and no further therapy pursued, the date when systemic treatment was discontinued was used in the TTNT analysis. Patients were otherwise censored at the time of last follow up.

Statistical analysis was carried out using JMP Pro, version 10. Survival analyses were performed using the Kaplan–Meier method with pair wise comparisons between treatment groups using the log-rank test, with P value of <0.05 were considered to be statistically significant. We excluded treatment groups with fewer than 10 patients in survival analyses.

Results

Study population

Table I shows the characteristics of the patients included in this study. Median follow up time for the study was 4.2 years. Most patients identified had limited stage (stage I-IIA) disease at the time of diagnosis and treatment (79.8%). The vast majority of the patients were diagnosed with MF (94.2%). Of the 223 patients, 135 were managed with SDT alone. Of the 88 patients that received some form of systemic therapy, patients with limited stage disease on average underwent two lines of treatment (range 1–8) while patients with extensive stage disease on average underwent three lines of treatment (range 1–7). As anticipated, patients with limited stage disease experienced a superior 3 year overall survival (94.8%) as compared to those with advanced-stage disease (54.8%).

Treatment analysis

Of the 88 patients treated with systemic treatments, we identified 214 different episodes of treatment with various agents: oral retinoids, interferon, chemotherapy, HDAC inhibitors, denileukin diftitox, and ECP (Supporting Information Table 1). Regarding the specific groups of systemic treatments, the oral retinoid treatment group included patients treated with acitretin, $n = 30$; bexarotene, $n = 36$; and isotretinoin, $n = 2$. The HDAC inhibitor group included patients treated with vorinostat ($n = 22$) and romidepsin ($n = 6$). The chemotherapy group included patients treated with either single agent [pralatrexate ($n = 9$), gemcitabine ($n = 14$), liposomal doxorubicin ($n = 6$), fludarabine ($n = 1$)] or
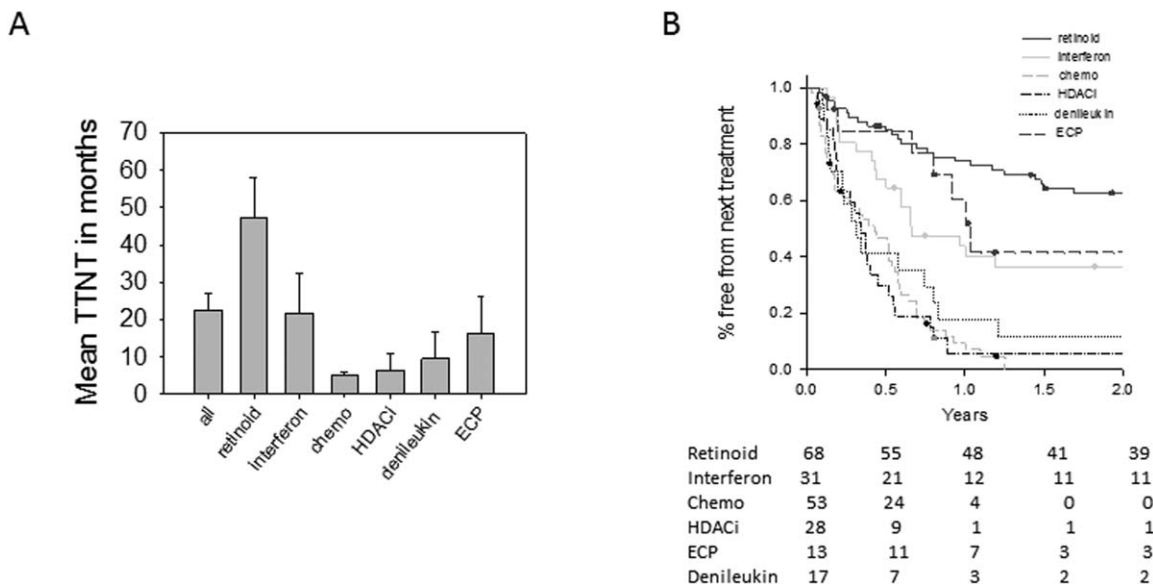

Figure 1. TTNT analysis for all stages. (A) Mean TTNT +/− CI for each treatment. (B) Kaplan–Meier curves for each treatment with *P* values from log rank comparisons shown in C. Both retinoids and interferon had a superior TTNT compared to the other therapies.
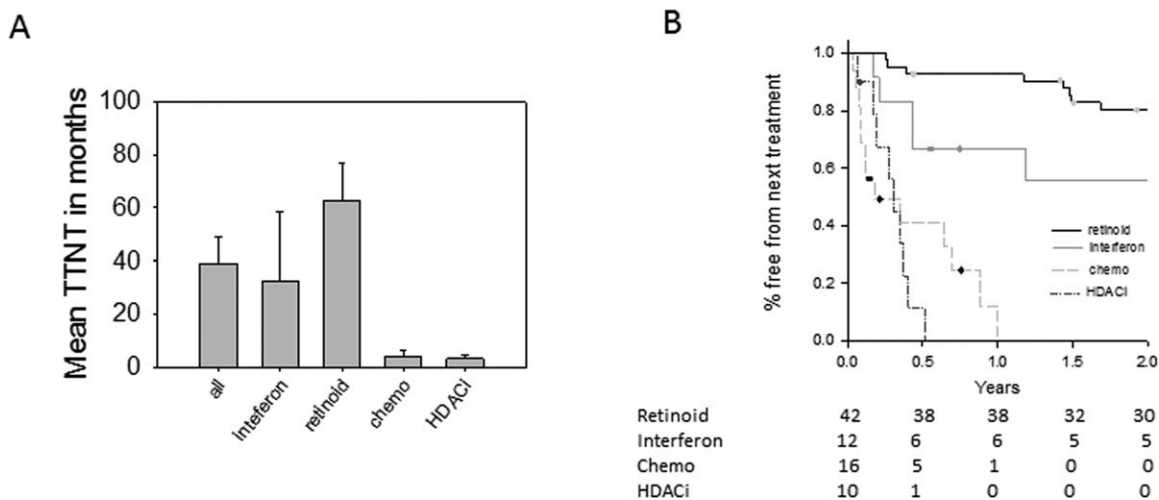
Figure 2. TTNT analysis for limited stage disease. (A) Mean TTNT +/− CI for each treatment. (B) Kaplan–Meier curves for each treatment with *P* values from log rank comparisons shown in C. Both retinoids and interferon had a superior TTNT compared to chemotherapy and HDAC inhibitors.
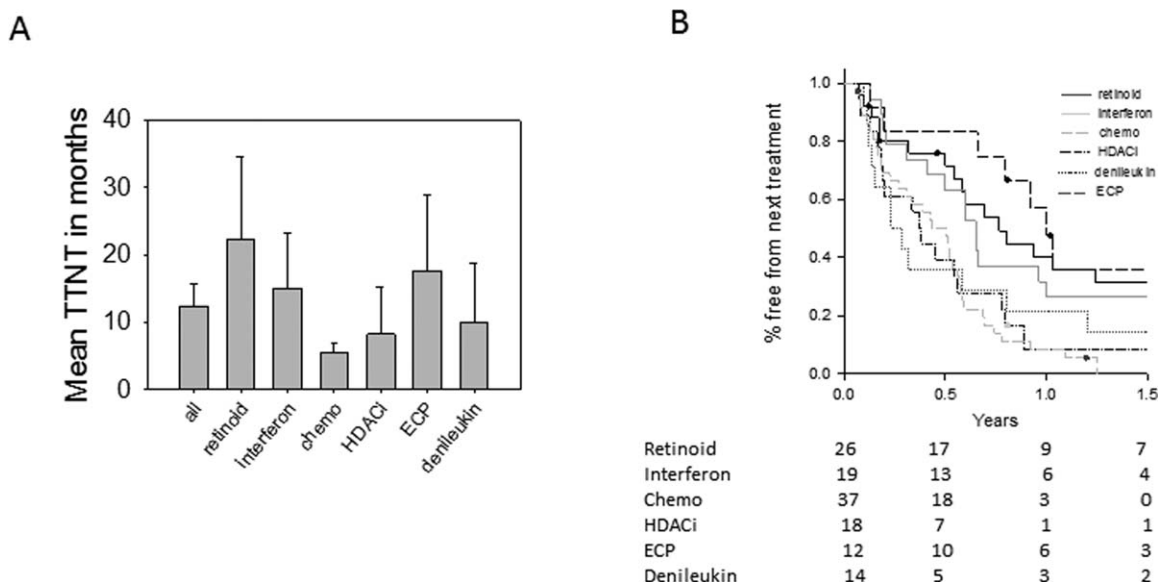

Figure 3. TTNT analysis for advanced stage disease. (A) Mean TTNT +/− CI for each treatment. (B) Kaplan–Meier curves for each treatment with *P* values from log rank comparisons shown in C. Retinoids and ECP had a superior TTNT compared to chemotherapy and HDAC inhibitors.

multi agent [(PEP-C [25] (*n* = 12), CHOP (*n* = 5), CVP (*n* = 1), CHOEP (*n* = 1), EPOCH (*n* = 1), and ICE (*n* = 1)] chemotherapy.

Oral retinoids were the most common therapy (31.8%), most often used in the setting of limited disease (61.8%) as a first line therapy. All other treatments (interferon, chemotherapy, HDAC inhibitors, denileukin diftitox, and ECP) were most frequently utilized in advanced stage disease. ECP was the most common first line treatment in SS (61.5%).

All treatments

Overall, retinoids were associated with the longest mean TTNT at 47.2 months and highest number of patients free from next treatment (FFNT) at 1 year (75.0%) which was superior to all treatments (Fig. 1, Supporting Information Table 2). Interferon had a relatively long TTNT at 21.7 months and was superior to chemotherapy and HDAC inhibitors. Chemotherapy had the shortest mean TTNT at 5.1 months and had a lower TTNT when compared to ECP, interferon, and retinoids. HDAC inhibitors also had a short mean TTNT at 6.4 months and had the lowest FFNT at 1 year (3.6%) This was inferior to all treatments except for chemotherapy and denileukin diftitox.

Denileukin diftitox had an intermediate TTNT (9.6 months), with 17.6% of patients who were FFNT at 1 year, suggesting heterogeneity in response among patients.

Limited stage disease

When comparing treatments in the setting of limited-stage disease, retinoids had the longest mean TTNT at 62.7 months with a FFNT at 1 year of 90.5% and was superior to all treatments, including interferon, HDAC inhibitors, and chemotherapy (Fig. 2, Supporting Information Table 3). Interferon had a superior TTNT compared to chemotherapy and HDACi at 32.6 months with a FFNT at 1 year of 50%. Both HDAC inhibitors and chemotherapy had relatively short TTNT in limited stage disease (3.3 months and 4.1 months, respectively). All limited stage disease patients failed therapy with HDAC inhibitors by 1 year, while only 6.2% of patients treated with chemotherapy were FFNT at 1 year.

Extensive stage disease

Among patients with advanced-stage disease, retinoids had the longest mean TTNT at 22.1 which was longer compared to

chemotherapy and HDACi (Fig. 3, Supporting Information Table 4). Both ECP and interferon had intermediate mean TTNT at 17.5 and 14.9 months, respectively, and both were associated with superior TTNT compared to chemotherapy, while ECP was also superior compared to HDACi. Denileukin diftitox had an intermediate mean TTNT at 10.0 months, but was not statistically significant compared to any of the other treatments. With denileukin diftitox, there were 3 of 14 patients who were FFNT at the end of 1 year, indicating a subset of patients who may have long term benefit with this therapy. As with limited stage disease, both chemotherapy and HDACi had relatively short mean TTNT, at 5.4 months and 8.2 months and low FFNTs at 6.2% and 0%, respectively.

We also examined TTNT following "early line" (1st and 2nd line of therapy) and "late line" (>2nd line of therapy) for interferon, HDAC inhibitors, and chemotherapy (data not shown). Retinoids were not included in the analysis as it was used very rarely as a late line treatment. We did not observe a statistically significant difference in the TTNT between early line and late line therapy.

■ Discussion

In this study, we retrospectively analyzed outcomes in systemically treated MF/SS patients from a single institution, including those treated with conventional chemotherapeutic agents, biologic response modifiers (e.g., retinoids and interferon), and HDAC inhibitors. There have been very few randomized clinical trials directly comparing commonly used therapies in MF/SS, making rational treatment decisions difficult. The increasing number of novel therapies currently available, or on the horizon, further compounds this challenge [14,26]. We used TTNT as a primary endpoint as this is a clinically meaningful surrogate that incorporates both disease progression and symptom control into a single endpoint. In addition, TTNT can be determined more accurately in a retrospective study than other objective endpoints, such as the modified Severity Weights Assessment Tool [27]. Disadvantages of TTNT include variability from clinician to clinician based on treatment practices and data skewing at a single institution due to a limited number of providers treating a rare disease.

We demonstrate that both chemotherapy and HDACi are associated with poor outcomes. For chemotherapy, the median TTNT is 5.1 months with 92.5% of patients requiring alternative therapy at 1 year. Long term responses were very few despite the respectable response rates reported with these agents in prior studies [11,28–30]. These results reiterate the very poor efficacy of chemotherapy in MF and SS, with no specific chemotherapeutic regimen providing a durable response. Increasing appreciation of the genetic landscape in these lymphomas demonstrates that alterations classically associated with resistance to conventional chemotherapeutic agents (e.g., loss of p53) are highly prevalent in CTCL [31–35]. In addition to these intrinsic mechanisms of resistance, extrinsic growth and survival factors provided by constituents of the tumor microenvironment likely promote chemotherapy resistance [36]. For HDAC inhibitors, the median TTNT is 6.4 months with 96.4% of patients requiring alternate therapy at 1 year. Very few durable responses were achieved with HDAC inhibitors. Multiple molecular mechanisms of HDAC inhibitor resistance have been proposed, including multidrug resistance gene

expression, NF-kappa B activation, and increased MAPK signaling [37,38]. Further elucidation of the mechanisms driving HDAC inhibitor resistance in CTCL may optimize the therapeutic potential of these novel agents. Collectively, the findings reported here are consistent with those reported by Hughes et al. [20]. In this large retrospective study, a similarly poor TTNT was observed with chemotherapy (3.9 months) and HDAC inhibitors (4.5 months).

In contrast, biologic response modifiers were well tolerated and associated with superior TTNT. In selected patients, retinoids, interferon, and ECP provided durable responses. Importantly, when retinoids and interferon were further analyzed in the setting of limited and extensive stage disease, their superior TTNTs persisted. Consistent with Hughes et al. [20], we did not find a difference in treatment effect between early line and late line interferon treated patients, suggesting interferon can be used with similar efficacy in treatment naïve patients and as a salvage option in more heavily pre-treated patients. These data support current guidelines recommending the use of retinoids and interferon in MF/SS.

This study has several limitations. Our sample sizes were generally quite small limiting the power of our study, particularly after stratifying patient groups based on disease stage. Although retinoids had a superior TTNT, they were predominantly used in patients with limited-stage disease, and at lower doses (data not shown) in patients undergoing SDT with UV irradiation. In addition, we cannot exclude selection bias, as patients initially presenting with bulky or rapidly progressive disease may have received chemotherapy of HDAC inhibitors leading to a shorter TTNT for these treatments. Treatment heterogeneity, particularly among conventional chemotherapeutic agents, and the small sample size preclude comparisons of specific agents. It is important to note that concurrent treatment with multiple agents, particularly retinoids, interferon, and ECP was not uncommon. The cases where the response to the first treatment was felt to be suboptimal and a second concurrent treatment was initiated were considered treatment failures. This may underestimate the apparent efficacy of these agents in our analysis. However, as retinoids, interferon, and ECP—the very treatments that were frequently used concurrently with other agents—were the treatments determined to have the highest TTNTs, we do not believe this limitation compromises our conclusions. If anything, this approach may underestimate the efficacy of these therapies that were associated with superior TTNT when compared with chemotherapy and HDAC inhibitors.

The therapeutic arsenal for MF and SS continues to expand. A number of novel agents are currently in development for both limited and extensive stage disease [14,26]. A number of immunotherapies are currently in clinical trials, including checkpoint blockade, antibody-drug conjugates (brentuximab vedotin, resimmune) [15,39], monoclonal antibodies (e.g., mogamulizumab) [40], and novel targeted agents [26,41]. Cytogenetic and genomic studies have revealed potential molecular targets [1,34,35]. However, extensive disease heterogeneity of MF/SS may suggest that future treatment approaches may need to be personalized, targeting specific molecular alterations and/or the tumor microenvironment. Clinical trial participation should be encouraged, as the TTNT is brief and few durable responses are achieved for most currently available agents.

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