Cutaneous T-cell Lymphomas: A Single-center Retrospective Analysis

Till Kaemmerer[1], Anne Guertler[1], Benjamin M. Clanner-Engelshofen[1], Corbinian Fuchs[1], Lars Einar French[1,2], Markus Reinholz[1]

[1]Department of Dermatology and Allergy, University Hospital, LMU Munich, Germany; [2]Dr. Phillip Frost Department of Dermatology & Cutaneous Surgery, University of Miami, Miller School of Medicine, Miami, USA

Corresponding author:
Till Kämmerer, MD
Department of Dermatology and Allergy
University Hospital, LMU Munich
Frauenlobstr. 9-11
till.kaemmerer@med.uni-muenchen.de

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ABSTRACT

Introduction: Cutaneous T-cell lymphomas (CTCLs) are rare diseases characterized by infiltration of malignant T-cells into the skin. We evaluated the prevalence, epidemiology, and therapy of CTCLs, focusing on its most well-known subtypes, namely mycosis fungoides (MF) and Sézary syndrome (SS).

Patients and methods: We retrospectively analyzed the medical data of patients with a histologically confirmed diagnosis of CTCL presenting to our outpatient department during a 5-year period from January 2015 to December 2019.

Results: We evaluated the files of 102 patients, of whom 67% were men and 33% women. The overall mean age was 59.1±14.1 (24-86) years. Ninety-two patients (90%) were diagnosed with MF and ten patients (10%) with SS. According to ISCL/EORTC, the majority of patients initially classified as stage IA (34%) and IB (45%). Disease frequency decreased at advanced stages (II: 4%; III: 7%; IV: 10%). Forty-five patients (44.1%) received only skin-directed therapy (SDT). Twenty patients (19.6%) progressed from SDT to systemic therapy (ST). Thirty-seven patients (36.3%) received ST combined with SDT (TS) from the start of treatment. Overall, fifty different therapeutic approaches of TS were initiated due to lack of response to therapy or disease progression.

Conclusion: Management of CTCLs aims to maintain patient quality of life while minimizing side-effects. As CTCLs are usually incurable diseases, the focus of treatment is on symptom control and prevention of disease progression. Due to the large patient group and the long observation period, our study allows for a valid evaluation of the frequency and therapy of MF and SS in a university outpatient clinic in Germany. We favor topical therapies in early stages with more invasive therapies in advanced stages.

KEY WORDS: CTCL, cutaneous T-cell lymphoma, retrospective, mycosis fungoides, Sézary syndrome

INTRODUCTION

CTCLs represent a rare group of malignant neoplasms characterized by aggressive T-cell infiltration into the skin. The mean age at disease onset is between 55 to 60 years. Men are affected more often than women (1.6:1 to 2:1), with an annual incidence of 0.5/100.000 (1,2). CTCL can present with a wide range of clinical symptoms, such as erythematous patches and plaques in earlier stages and nodal tumor

infiltration in later stages. The vast variety of symptoms complicates diagnosis, especially in early stages, as cutaneous T-cell lymphomas can imitate other skin disorders such as eczema, morphea, psoriasis, and pityriasis rubra pilaris (3).

In 2007, the staging system for CTCLs underwent a revision by the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organisation of Research and Treatment of Cancer (EORTC). It replaced the original guidelines from the Mycosis Fungoides Cooperative Group (MFCG) from 1979 and integrated advances in tumor-cell biology, immunohistochemistry, and radiologic imaging (4,5). The most well-known subtypes of CTCLs are MF and SS. Further subtypes are erythrodermic MF, parapsoriasis, and cutaneous CD30+ lymphoproliferative disorders such as lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (pcALCL), and indeterminate cases. MF is characterized by erythematous patches, plaques, and skin-tumors. Involvement of blood, lymph nodes, and, rarely, other organs is possible. Diagnosis is complicated and prolonged, taking up to six years due to its similarity in the early stages to benign inflammatory skin diseases (6,7). MF is typically non-aggressive; about 80% of patients have a regular life expectancy. A minority of patients with MF experience disease progression with lymph node involvement and skin tumors (2). SS shows erythroderma accompanied by malignant lymphocytes in the blood (>5% circulating Sézary cells) and lymph nodes. Usually, it is resistant towards therapy, leading to a median survival rate of three years due to early immune suppression and death from infection (8). Clinical assessment of MF/SS includes evaluation of the type and extent of skin involvement, occurrence of palpable nodes, examination of peripheral blood by molecular analysis, and flow cytometry. Except for early stages with limited skin involvement (IA-IIA), radiologic examination is recommended for initial staging to evaluate internal organ involvement. A skin biopsy is essential in order to establish diagnosis and to evaluate large cell-transformation, immunophenotyping, and the presence of T-cell receptors (9).

Current treatment options in early-stage disease are mainly skin-directed therapies such as topical corticosteroids, topical retinoids, extracorporeal photopheresis (ECP), psoralen and ultraviolet A (PUVA), radiotherapy, and ultraviolet phototherapy (UVB). In advanced stages, skin-directed therapies are usually combined with systemic approaches, such as retinoids, immunotherapy, and chemotherapy. Thus far, all available therapies have been only palliative, with the exception of stem cell transplantation (10).

In this study, we analyzed and summarized the clinical characteristics and therapies in a cohort of 102 patients with both clinical and histological diagnosis of CTCLs presenting to our outpatient clinic between 2015 and 2019. We focused on epidemiologic factors such as ISCL/EORTC classification, disease progression under topical and systemic treatment, and the duration of each therapy. Through this, we aimed to provide insight into the therapy of CTCLs at our university outpatient clinic and, given the multiple treatment options, to highlight which therapies achieve the longest progression-free outcome possible based on our experience.

PATIENTS AND METHODS

Data acquisition

After receiving ethical approval (ethics committee of the medical faculty at LMU, Munich/Germany, Ref.-No. 20-579), patient data were collected using electronic records containing the patients' medical history, laboratory results, and assessment of photo documentation. Retrieved data for each patient were TNMB staging, treatment modalities up to the third line therapeutic approach, and duration of treatment.

Selection of patients and staging

Between January 2015 and December 2019, 247 patients presented to the CTCL-outpatient clinic of the Department of Dermatology and Allergy, University Hospital, LMU Munich, Germany. After correlating clinical, histological, and immunochemical results, 102 patients with MF and SS were included for evaluation. The retrospective staging of TNMB was

Table 1: Staging of MF/SS according to ISCL/EORTC.

	T1	T2	T3	T4
NM Classification	Limited Patch/Plaque	Generalized Patch/Plaque	Tumor	Erythroderma
N0 M0	IA	IB	IIB	IIIA
N1 M0	IIA	IIA	IIB	IIIB
N2-3 M0	IVA	IVA	IVA	IVA
N0-3 M1	IVB	IVB	IVB	IVB

Table 2: Epidemiologic patient characteristics.

	Overall	Mycosis fungoides (MF)	Sezary Syndrome (SS)
	n=102	n=92	n=10
Age (years)	60.5 (24-86)	60 (24-86)	68 (49-83)
Male	68 (66.7 %)	62 (67.4 %)	6 (60.0 %)
Female	34 (33.3%)	30 (32.6%)	4 (40%)
Follow up (month)	26 (3-60)	27 (3-60)	17 (7-53)

performed according to the classification by ISCL/EORTC from 2007, as described in Table 1 for 102 patients with MF (n=92) and SS (n=10). Patients underwent a physical examination, complete blood cell count with examination for Sézary cells, a general blood chemistry panel, and skin biopsy. Patients with palpable lymph nodes underwent nodal ultrasound. Additional imaging was conducted in patients with advanced skin involvement or suspicious lymph nodes. All skin biopsies were classified according to ISCL with superficial lymphoid infiltrate with epidermotropism and/or atypia.

Disease progression

We defined disease progression as a lack of response to therapy with the primary endpoint as time to next treatment (TTNT). Therapy was graded into two interventional stages: the first stage was defined as skin-directed therapies (SDT), including topical therapy with steroids (TO, topical only) and interventional topical therapy with ECP, PUVA, radiotherapy, and UVB. The second stage was defined as systemic therapy (ST) with interferons, retinoids, immunotherapy, and chemotherapy. When the second stage of SDT or systemic therapy was added to a singular topical therapy or a switch of systemic therapy occurred, this was classified as disease progression and TTNT.

Statistical analysis

To analyze the available data of 102 patients, a table with 26 parameters was compiled using the statistics software IBM SPSS Statistics for Windows, Version 26.0 (IBM Corporation, Armonk, NY, USA). Each data set was numerically encoded to allow statistical analysis. Patient data was evaluated anonymously. Descriptive data were represented by absolute and relative frequency, and additionally in part by mean values, median values, and standard deviation., Frequency tables and graphs were generated using the descriptive data. Cross tables were used to investigate the interrelations between two variables, and absolute and relative frequency for the individual subgroups were determined. two features were tested for independence using the chi-square test.

RESULTS

Patient characteristics

We summarized patient characteristics in Table 2. The male-to-female ratio was 2:1. Average age at presentation was 60.5 years and ranged from 24 to 86 years. Diagnosis of MF (90%) was more frequent than SS (10%) and associated with a younger age. The median duration of treatment at our outpatient department for MF was 27 months (range, 3-60 months),

Table 3: Summary of Demographic and Clinical Staging Characteristics According to ISCL/EORTC Classification.

Staging		n	Age (years)		Male		Female		Mycosis fungoides (MF)		Sèzary Syndrome (SS)	
Overall		102	60.5	(24-86)	68	(67 %)	34	(33%)	92	(90 %)	10	(10 %)
I	**IA**	35 (34 %)	64	(24-86)	23	(67 %)	12	(33 %)	35	(100 %)	0	
	IB	46 (45 %)	56	(26-81)	33	(70 %)	13	(30 %)	46	(100 %)	0	
II	**IIA**	0	0		0	0	0		0		0	
	IIB	4 (4 %)	59.5	(55-60)	2	(50 %)	2	(50 %)	4	(100 %)	0	
III	**IIIA**	3 (3 %)	71	(67-77)	2	(67 %)	1	(33 %)	3	(60 %)	0	
	IIIB	4 (4 %)	63.5	(58-69)	3	(67 %)	1	(33 %)	4	(67 %)	0	
IV	**IVA1**	3 (3 %)	78	(66-84)	1	(33 %)	2	(67 %)	0		3	(100 %)
	IVB	7 (7 %)	68	(62-83)	4	(57 %)	3	(43 %)	0		7	(100 %)

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17 months for SS (range, 7-53 months) until patient death or being lost to follow-up. Median age distribution by ISCL/EORTC classification demonstrated that patients with early-stage disease were younger on average than those in later stages, as shown in Table 3. The majority of our 102 patients had stages IA (34%) or IB (45%), which are defined by limited or generalized patches and plaques as shown in Table 1. With disease progression and increasing severity, we observed a decrease in the number of patients, as shown in Table 3. Due to the limited number of patients, we decided not to differentiate between the subgroups of stage II and combined stage III and IV.

Treatment analysis

All 102 patients with MF and SS received topical steroids combined with moisturizers as basic treatment. Table 4 shows combination of SDT and ST in patients staged according to ISCL/EORTC. Forty-five patients (44.1%) received SDT. Twenty patients (19.6%) progressed from SDT to ST, thirty-seven patients (36.3%) received ST from the start of the treatment, and fifty different approaches of TS were initiated due to lack of response. At early stages IA and IB, patients predominantly underwent skin-directed therapy, with rising numbers of systemic approaches in advanced stages. As shown in Table 4, stage IA was mainly treated by topical steroids only (TO, 74.3%), with fewer additional SDT (phototherapy, 11.5%; alitretinoin, 8.6%; radiotherapy 2.9%). Second treatment attempts did not occur at this stage. In stage IB patients, decreased use of TO (36.2%) and a rising number of additional SDT (phototherapy, 36.1%; alitretinoin, 10.6%) were observed. First-line systemic therapies were MTX (6.4%) and a combination of ECP, alitretinoin, and INF-α (2.1%). The second- and third-line therapies were the more invasive treatments ECP and INF-α. At stage II, only 28.6% were initially treated with TO and additional skin directed therapies (phototherapy 14.3%). However, more invasive treatments such as ECP (28.6%), a combination of ECP and alitretinoin (14.3%), and bexarotene (14.3%) were implemented. Second and third treatment lines also showed rising use of radiotherapy and combinations of skin-directed and systemic therapies. In contrast to the earlier stages, TO was no longer used in stages III and IV, but more intensive skin-directed therapies (PUVA) and systemic therapies (chemotherapy, ECP, alitretinoin) as well as combined SDT approaches were observed. These two stages were combined due to the small number of patients (stage III n=7, stage IV n=10).

Table 4: Distribution of first three treatment lines in different disease stages according to ISCL/ERTOC.

Stages	IA			IB			II			III, IV		
TA	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Topical	26 (74%)	0	0	17 (36%)	0	0	2 (29%)	0	0	0	0	0
ECP	1 (3%)	0	0	1 (2%)	1 (7%)	1 (11%)	2 (29%)	0	0	1 (7%)	2 (25%)	0
PUVA	1 (3%)	0	0	12 (26%)	4 (29%)	2 (22%)	1 (14%)	0	0	5 (36%)	2 (25%)	0
RT	1 (3%)	0	0	0	2 (14%)	0	0	2 (50%)	0	0	0	0
UVB	3 (9%)	0	0	5 (11%)	2 (14%)	0	0	0	0	1 (7%)	0	0
Bexarotene (B)	0	0	0	0	0	0	1 (14%)	0	1 (33%)	0	0	0
CT	0	0	0	0	0	0	0	0	1 (33%)	1 (7%)	1 (13%)	1 (20%)
INF-α	0	0	0	0	0	2 (22%)	0	0	1 (33%)	0	0	0
MTX	0	0	0	3 (6%)	0	2 (22%)	0	0	0	0	0	0
Altretinoin (A)	3 (9%)	0	0	5 (11%)	1 (7%)	1 (11%)	0	1 (25%)	0	3 (21%)	1 (13%)	0
PUVA + A	0	0	0	0	0	0	0	0	0	1 (7%)	0	0
INF-α + A	0	0	0	0	1 (7%)	0	0	1 (25%)	0	0	0	1 (20%)
INF-α + PUVA	0	0	0	0	1 (7%)	0	0	0	0	0	0	0
INF-α + UVB	0	0	0	0	0	0	0	0	0	1 (7%)	0	0
ECP + A	0	0	0	3 (6%)	1 (7%)	0	1 (14%)	0	0	1 (7%)	2 (25%)	2 (40%)
ECP + B	0	0	0	0	0	0	0	0	0	0	0	1 (20%)
ECP + A + INF-α	0	0	0	1 (2%)	0	0	0	0	0	0	0	0
ECP + INF-α	0	0	0	0	1 (7%)	0	0	0	0	0	0	0
MTX + A	0	0	0	0	0	1 (11%)	0	0	0	0	0	0

Abbreviations: A, alitretinoin; CT, chemotherapy; ECP, extracorporeal photopheresis; EORTC, European Organisation for Research and Treatment of Cancer; INF-α, interferon alpha, ISCL, International Society for Cutaneous Lymphomas; MTX, methotrexate; PUVA, psoralen and ultraviolet A; RT, radiotherapy; TA, therapeutic approach; TO, topical only; UVB, ultraviolet light phototherapy B.

Time to next treatment

The combination of ECP and alitretinoin as the first therapeutic approach was associated with the longest median TTNT of 34.5 months. MTX (15 months), ECP (12 months), the combination of UVB/INF-α (12 months), and alitretinoin (10 months) were superior to PUVA (2 months), UVB (2 months), PUVA/alitretinoin (6 months), ECP/alitretinoin/INF-α (7 months), and bexarotene (1 month), as shown in Figure 1. For the second therapeutic approach, the combination of ECP and alitretinoin had the longest median TTNT (20 months), followed by the combination of ECP/INF-α (15 months), INF-α/alitretinoin (12.5 months), UVB (12 months), and INF-α/PUVA (12 months), as shown in Figure 2. These were superior in TTNT to ECP (3.5 months), PUVA (2 months), and radiotherapy (1 month). The third therapeutic approach showed the highest TTNT for ECP (9 months), followed by MTX (7.5 months), and INF-α/alitretinoin (6 months), which were superior to INF-α (5 months) and alitretinoin/MTX (3 months), as shown in Figure 3.

DISCUSSION

We present the results of a retrospective longitudinal cohort study on patients with MF and SS diagnosed and treated at our university outpatient clinic from January 2015 to December 2019. Similar to Hanel *et al.*, we chose TTNT as the primary endpoint because it is a compelling surrogate that combines both disease progression and symptom control into a single endpoint (11). In addition, end points can be more accurately determined in a retrospective study than, for example, with the commonly used Modified Severity-Weighted Assessment Tool (12). A disadvantage of TTNT as an endpoint is the variability of treatment due to the availability of only a few experts with different clinical experience and treatment practice that were treating a rare disease with large therapeutic variation (11).

We report a large heterogeneity of nineteen different therapeutic approaches used as first-line treatment, depending on disease severity and progression at first consultation. This can be explained by the limitation of eligible drugs and the rarity of the diseases, which affects retrospective evaluation and the development of uniform treatment guidelines (13). As a result, treatment recommendations are based on facility preferences and equipment, physician skills, and availability of treatment options (14). The most important criterion for the choice of treatment of CTCLs according to guideline recommendations is the TNMB stage (15). However, in the context of the regularly slowly progressive disease, possible therapy-associated side-effects should also be taken into account so that the most effective and low-risk therapy possible can be used (16,17). Most of our patients had initial stages of CTCL with disease limited to the skin. With disease progression, the number of patients decreased with the diagnosis of stages III and IV. Our epidemiologic data are consistent with previous studies comparing sex, age at disease onset, and the proportion of different stages of disease manifestation (2,14,18).

Stage IA was most frequently treated by skin-directed approaches (topical steroids, phototherapy), followed by singular systemic approaches (ECP, alitretinoin). This earliest manifestation stage typically remains stable for a long time, without the need for therapeutic changes (19). We did not note treatment changes at this stage, which means the stages remained stable or a direct change to a further stage occurred within the observation period.

In stage IB, there were fewer approaches using topical therapy alone, with an increasing number of additional skin-directed therapies (phototherapy, radiotherapy). Systemic approaches such as ECP, INF-α, MTX, and combinations of ECP, alitretinoin, and INF-α have been used. This reflects the wide range of potential therapeutic options for CTCL treatment in clinical guidelines (13,14,16), whereby, as shown in Table 4, the more intense and potentially more side-effect-rich therapies are used in the second and third line. We would like to emphasize that therapy should be extended in accordance with the guidelines in the event of progression, but the focus should also be on therapies with as few side-effects as possible. In addition to PUVA, we favor the use of the retinoid alitretinoin or, in more severe cases, the administration of MTX (10).

As the disease progresses, the use of systemic therapy at our center also expanded. Use of additional skin-directed therapies such as ECP, radiotherapy, and combinations of systemic and topical approach-

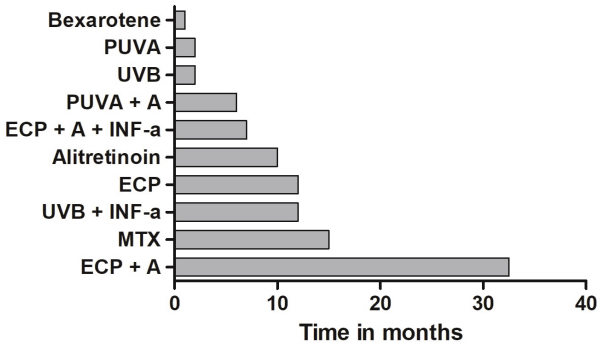

Figure 1. Distribution of therapies in the first therapeutic approach according to time to next treatment (TTNT) in months.

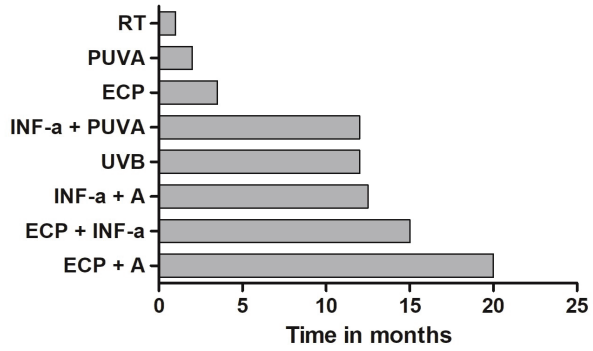

Figure 2. Distribution of therapies in the second therapeutic approach according to time to next treatment (TTNT) in months.

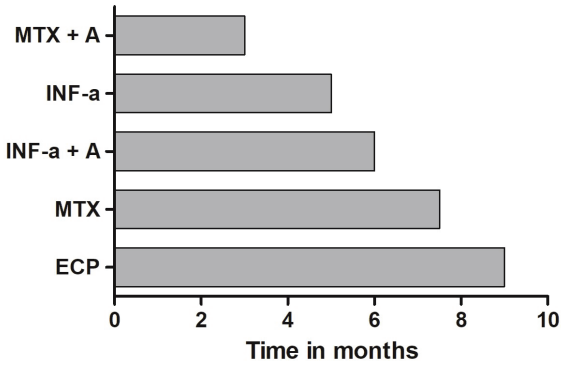

Figure 3. Distribution of therapies in the third therapeutic approach according to time to next treatment (TTNT) in months.

es increased. Our data support the preferential use of more invasive treatment algorithms as first-line therapy for patients at advanced and resistant disease stages (10,11).

Another focus of our study was the evaluation of TTNT in different therapies. Measured using TTNT, we observed an advantage in the combination of ECP and oral alitretinoin in first (TTNT = 34.5 months) and second line systemic therapeutic approaches (TTNT = 20 months). Retinoids for the treatment of CTCL have been used for decades as monotherapy or in combination due to their advantageous safety profile (20). As derivatives of vitamin A, they modulate cell differentiation, immunoregulation, and proliferation of epithelial cells and the mononuclear skin infiltrate (21). The biologic effects of retinoids are mediated by two distinct families of intracellular receptors: older retinoids bind to retinoic acid receptors (RARs), whereas bexarotene was developed for binding to the retinoic X receptors in CTCL treatment (RXR) (22). Alitretinoin binds to RAR and RXR and is described as having a potentially more favorable safety profile compared with other vitamin A derivates such as bexarotene or acitretin regarding mucocutaneous side-effects and laboratory findings of serum cholesterol, triglycerides, and thyroid parameters (23). Similar to previous reports, we found better response for alitretinoin in combination with additional agents compared with other therapies. We noted similar limitations in our report due to the small and inconsistent cohort, which cannot be considered representative. None of our patients were treated with alitretinoin alone, but only in combination with other agents (24,25). Bexarotene was very rarely administered at our institution, so we cannot perform an assessment of its efficacy.

Furthermore, we found promising response rates with MTX and different combinations of ECP and INF-α. MTX as a folic acid antagonist binds competitively to dihydrofolate reductase and has antiproliferative effects due to interfering with the replication of cells. Myelosuppression, acute renal failure, and pulmonary toxicity are just some of the side-effects (26). INF-α suppresses Th2 cytokine production from malignant lymphoma cells and activates CD8+ and NK cells. Side-effects include flu-like symptoms, myelosuppression, and diarrhea (27,28). Both drugs have long been recognized as useful therapeutics in the treatment of malignant cutaneous lymphoproliferative disorders and show good TTNT in comparison (29). INF-α in particular is usually well-tolerated and associated with a superior TTNT in previous reports (11). Unfortunately, there has been a shortage of INF-a, so that this therapy is currently losing importance. In summary, we agree with the recommendations of the guidelines and recommend cautious therapy with low disease activity to avoid potential side-effects.

The main limitations of the present study were retrospective data collection and small sample size, especially for advanced stages. Retrospective data collection often lacks data on potential confounders, leading to overinterpretation, differential loss to follow-up, and potential bias in retrospective data analysis. Because our evaluation refers to the TTNT of different therapies, regardless of disease stage, we cannot make specific statements about specific treatment recommendations. Therefore, this analysis is intended as an overview rather than a guide. Additionally, combination therapies were frequently used, which makes it difficult to evaluate the individual effects of each therapeutic.

CONCLUSION

This monocentric retrospective study demonstrated wide variability in treatment approaches at different stages of MF and SS. The number of different therapies and their frequent changes and adaptations reflect the difficulty of CTCL therapy and its potentially progressive course dynamics. We advocate

for the use of skin-targeted therapies at early stages and combinations of therapies at advanced stages. Nevertheless, this retrospective study on the efficacy of different therapies in this patient cohort was limited because a large number of therapies were combined, making it difficult to assess the efficacy of single therapies. The combination of ECP with alitretinoin showed promising results in our cohort. Future studies with prospective, randomized, controlled clinical trials are needed to verify this and to provide clinical guidelines for advanced disease stages.

Ethical approval:

This study has been approved by the local ethics committee (ethics committee University Hospital Munich, LMU, Munich/Germany, Ref.-No. 20-579).

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Abbreviations:

CD – Cluster of Differentiation

CTCL – Cutaneous T-cell lymphomas

ECP – Extracorporeal photopheresis

EORTC – European Organisation of Research and Treatment of Cancer

INF-α – Interferon alpha

ISCL – International Society for Cutaneous Lymphomas

LyP – Lymphomatoid papulosis

MF – Mycosis fungoides

MTX – Methotrexate

pcALCL – Primary cutaneous anaplastic large cell lymphoma

PUVA – Psoralen and ultraviolet A

SS – Sézary syndrome

ST – Systemically and topical therapy combined from beginning

TO – Topical therapy only

TS – Topical and systemic therapy combined after progression

UVB – Ultraviolet light phototherapy B

References:

1. Bagherani N, Smoller BR. An overview of cutaneous T cell lymphomas. F1000Res. 2016;5.
2. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol. 2003;139:857-66.
3. Ghazawi FM, Alghazawi N, Le M, Netchiporouk E, Glassman SJ, Sasseville D, *et al.* Environmental and Other Extrinsic Risk Factors Contributing to the Pathogenesis of Cutaneous T Cell Lymphoma (CTCL). Front Oncol. 2019;9:300.
4. Lamberg SI, Bunn PA, Jr. Cutaneous T-cell lymphomas. Summary of the Mycosis Fungoides Cooperative Group-National Cancer Institute Workshop. Arch Dermatol. 1979;115:1103-5.
5. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, *et al.* 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;110:1713-22.
6. Fujii K. New Therapies and Immunological Findings in Cutaneous T-Cell Lymphoma. Front Oncol. 2018;8:198.
7. Kirsch IR, Watanabe R, O'Malley JT, Williamson DW, Scott LL, Elco CP, *et al.* TCR sequencing facilitates diagnosis and identifies mature T cells as the cell of origin in CTCL. Sci Transl Med. 2015;7:308ra158.
8. Blaizot R, Ouattara E, Fauconneau A, Beylot-Barry M, Pham-Ledard A. Infectious events and associated risk factors in mycosis fungoides/Sezary syndrome: a retrospective cohort study. Br J Dermatol. 2018;179:1322-8.
9. Foss FM, Girardi M. Mycosis Fungoides and Sezary Syndrome. Hematol Oncol Clin North Am. 2017;31:297-315.
10. Oka T, Miyagaki T. Novel and Future Therapeutic Drugs for Advanced Mycosis Fungoides and Sezary Syndrome. Front Med (Lausanne). 2019;6:116.
11. Hanel W, Briski R, Ross CW, Anderson TF, Kaminski MS, Hristov AC, *et al.* A retrospective comparative outcome analysis following systemic therapy in Mycosis fungoides and Sezary syndrome. Am J Hematol. 2016;91:E491-E5.
12. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, *et al.* Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011;29:2598-607.
13. Hughes CF, Khot A, McCormack C, Lade S, Westerman DA, Twigger R, *et al.* Lack of durable disease

control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. Blood. 2015;125:71-81.

14. Quaglino P, Maule M, Prince HM, Porcu P, Horwitz S, Duvic M, *et al.* Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium. Ann Oncol. 2017;28:2517-25.
15. Trautinger F, Knobler R, Willemze R, Peris K, Stadler R, Laroche L, *et al.* EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer. 2006;42:1014-30.
16. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, *et al.* Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J Clin Oncol. 2015;33:3766-73.
17. Dippel E, Assaf C, Becker JC, von Bergwelt-Baildon M, Beyer M, Cozzio A, *et al.* S2k-Leitlinie - Kutane Lymphome Update 2016 - Teil 2: Therapie und Nachsorge (ICD10 C82 - C86). J Dtsch Dermatol Ges. 2018;16:112-23.
18. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, *et al.* Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010;28:4730-9.
19. Dugas-Breit S, Schulze HJ, Hallermann C. New and established treatment options for mycosis fungoides and Sezary syndrome - an update. J Dtsch Dermatol Ges. 2014;12:561-9.
20. Zackheim HS. Cutaneous T cell lymphoma: update of treatment. Dermatology. 1999;199:102-5.
21. Sokolowska-Wojdylo M, Lugowska-Umer H, Maciejewska-Radomska A. Oral retinoids and rexinoids in cutaneous T-cell lymphomas. Postepy Dermatol Alergol. 2013;30:19-29.
22. Wagner CE, Jurutka PW, Marshall PA, Groy TL, van der Vaart A, Ziller JW, *et al.* Modeling, synthesis and biological evaluation of potential retinoid X receptor (RXR) selective agonists: novel analogues of 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethynyl]benzoic acid (bexarotene). J Med Chem. 2009;52:5950-66.
23. Ruzicka T, Larsen FG, Galewicz D, Horvath A, Coenraads PJ, Thestrup-Pedersen K, *et al.* Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. Arch Dermatol. 2004;140:1453-9.
24. Kapser C, Herzinger T, Ruzicka T, Flaig M, Molin S. Treatment of cutaneous T-cell lymphoma with oral alitretinoin. J Eur Acad Dermatol Venereol. 2015;29:783-8.
25. Kaemmerer T, Stadler PC, Helene Frommherz L, Guertler A, Einar French L, Reinholz M. Alitretinoin in the treatment of cutaneous T-cell lymphoma. Cancer Med. 2021;10:7071-8.
26. Olsen EA. The pharmacology of methotrexate. J Am Acad Dermatol. 1991;25(2 Pt 1):306-18.
27. Wain T, Pavli A, Wells J, Fernandez-Penas P. The efficacy and safety of methotrexate versus interferon in cutaneous T-cell lymphomas. J Dermatolog Treat. 2018;29:715-9.
28. Alpdogan O, Kartan S, Johnson W, Sokol K, Porcu P. Systemic therapy of cutaneous T-cell lymphoma (CTCL). Chin Clin Oncol. 2019;8:10.
29. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol. 2014;70:205 e1-16; quiz 21-2.