Mycosis Fungoides: A 10-year Turkish Experience

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ABSTRACT Mycosis fungoides is the most common primary cutaneous T cell lymphoma, characterized by erythematous patches and plaque lesions with slow progression to cutaneous tumors or extracutaneous involvements in some patients. We aimed to evaluate the clinical characteristics, treatment responses, disease courses, and mortality rates of our MF cases. The data of 100 patients with MF were retrospectively examined from medical records in our clinic between January 2005 and January 2015. Demographic and clinical characteristics of the patients, disease stage, treatment protocols, response to treatment, recurrence, progression, and mortality rates were recorded. The male to female ratio in patients was 1.2. Mean age at onset of disease was 46, and duration of disease ranged from one to 42 years. At time of diagnosis 31 patients were at stage 1A, 31 at stage 1B, 30 at stage 2A, 2 at stage 2B, 1 at stage 3, and 5 at stage 4. Stable disease was observed in 35% of patients, progression in 10%, relapse in 27%, and complete response in 28%. Large cell transformation was found in 3 patients and additional malignity in 11. Thirty-seven patients (37%) were still surviving disease-free. 10 patients had died, three of them due to disease-related conditions. The most common first-line therapy in our study was phototherapy. It was applied to 87% of patients from stage 1A. Our results are generally consistent with current literature, but disease progression and disease-specific mortality rates were significantly lower than the literature, probably due to early phototherapy.

KEY WORDS: mycosis fungoides, disease progression, relapse, survival

INTRODUCTION

Cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin lymphomas characterized by clonal diffusion of neoplastic T-cells in the skin. The most common type is mycosis fungoides (MF), which constitutes approximately 50% of CTCLs (1). The global incidence of MF is 0.36-0.64/100,000, and mean age at time of diagnosis is 55-58 (1,2).

There is still no curative treatment for MF. Therefore, the objective of treatment is to improve patients' quality of life, to ameliorate symptoms by minimizing treatment toxicity, and to achieve and maintain remission (3). Patient characteristics, comorbidities, and prognostic markers are important in treatment selection (2).

In contrast to other lymphoproliferative diseases in which cytogenetic and laboratory findings play a decisive role, in MF TNMB (tumor, node, metastasis, and blood) staging is still an important prognostic

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factor for selection of risk-based therapy (4,5). Most patients with MF are in the limited disease stage at diagnosis (6). Tumoral lesions (T3), erythroderma (T4), nodal involvement with partial or complete destruction (N3), organ metastasis (M1), or severe leukemic involvement (B2) are seen in advanced stages of the disease (4).

Skin-targeted therapies are the first choice for treatment in early stages. These treatments include topical corticosteroids, topical chemotherapy agents (nitrogen mustard, carmustine), topical retinoids, topical imiquimod, narrowband ultraviolet B (nbUVB), psoralen and ultraviolet A (PUVA), radiotherapy, and total skin electron irradiation. Systemic treatments include biological agents, immunomodulators, chemotherapeutic agents, stem cell transplantation, and extracorporeal photopheresis (7).

The purpose of this study was to analyze the demographic characteristics, treatment selection, responses, clinical course, and mortality rates in cases of MF from our center in northeastern Turkey.

PATIENTS AND METHODS

We retrospectively reviewed the data of patients who were diagnosed with MF at our Department of Dermatology, Trabzon, Turkey between January 2005 and January 2015. 130 patients with histopathological results and ICD codes compatible with MF were included in the study. However, non-MF CTCL was present in 15 of these patients. Another 15 patients were excluded from the study due to lack of clinical follow-up after diagnosis. Finally, 100 patients clinically and histopathologically confirmed with MF were enrolled. Disease stages for all patients, agents used in treatment, responses to treatments, recurrence, progression, and mortality rates were recorded and correlations were evaluated.

Patients were staged according to the EORTC. Course of disease was examined under four headings – complete remission, stable disease, progression (advanced stage, excluding mortality) or relapse. Stable disease was defined as a lack of progression to the next clinical stage. Progression was defined with pathologic lymph nodes indicating advanced stage progression (≥2B). Lactate dehydrogenase (LDH) levels, total IgE levels, peripheral blood eosinophil counts, and Sezary cells at time of diagnosis were recorded. Causes of death were confirmed from clinical records or by contacting relatives. Treatments received, doses, duration of treatment, doses, accompanying systemic comorbid conditions, malignancies, and superficial lymph node ultrasonography findings of the axillary and inguinal lymph nodes were evaluated. In the presence of palpable lymphadenopathy, lymph node ultrasonography were carried out routinely in our clinic. Biopsy was performed if there was a pathologic lymph node on ultrasonography. For the evaluation of response to treatment, control biopsies and clinical examination records from patients were reviewed.

The data were analyzed on SPSS (Statistical Packages for Social Analysis) version 13.0 software. Measurements of data were expressed as mean ± standard deviation, and numerical data as number (%). The chi square test was applied to analyze relations between two variables.

RESULTS

Patient data

Hundered cases diagnosed with MF between January 2005 and January 2015 were enrolled. The ratio of women to men was 0.85, and patient ages ranged between 16 and 95. Mean age at onset of disease was 46, and mean time from onset of symptoms to diagnosis was 1.89±2.61 years. Duration of disease ranged between one to 42 years (mean 11.36±8.95). The mean follow-up period of the patients was 5.26±2.36 years. Previous diagnosis of non-specific dermatitis was present in 6 patients, and previous history of parapsoriasis confirmed by biopsy was present in 10. Seven of the patients had parapsoriasis diagnosed as large plaque parapsoriasis based on the clinical features of the lesion (Table 1).

Table 1. Demographics of 100 patients with mycosis fungoides

Women/men (n)	46/54
Mean age ± SD (year)	46.29±16.54
Time to diagnosis ± SD (year)	1.89±2.61
Duration of disease (years)	1-42
Parapsoriasis (n)	10
Malignancy (n)	11
Large cell transformation (n)	3
Mortality (n)	10

*SD: Standard deviation

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Table 2. Therapeutic approaches based on the of clinical stage of the disease

	Stage 1A	Stage 1B	Stage 2A	Stage 2B	Stage 3	Stage 4
Topical steroids*	100.0%*	100.0%*	100.0%*	-	-	-
Phototheraphy alone	90.4%	84.5%	77.1%	-	-	-
Phototheraphy and interferon	-	6.2%	14.2%	67,8%	-	17.0%
Phototheraphy and retinoids	-	-	5.7%	16,6%	-	-
Topical imiquimod	3.2%	6.2%*	-	-	-	-
Topical retinoid	3.2%	3.1%*	2.8%*	-	-	-
Interferon	-		-	-	-	-
Bexarotene	-	-	-	16,6%	-	-
Acitretin	-	-	-	-	-	-
Local radiotherapy	3.2%	-	-	-	-	-
Total skin electron beam therapy	-	-	-	-	-	-
Extracorporeal photopheresis	-	-	-	-	100.0%	-
Monochemotherapy	-	-	-	-	-	-
Polichemotherapy[a]	-	-	-	-	-	83.0%

*Adjuvant therapy

[a]CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)

Stage, progression, relapses

Fifty-seven patients had patch lesions, 27 had plaques, 10 patients had tumoral lesions, and 6 patients were erythrodermic. Thirty-one patients (31%) were stage 1A at time of diagnosis, 31 (31%) were stage 1B, 30 (30%) were stage 2A, 2 (2%) were stage 2B, 1 (1%) was stage 3, and 5 (5%) were stage 4. Stable disease was found in 35 patients, progression in 10, relapse in 27, and complete response in 28. In stage 1A cases stable disease was found in eight, progression in one, complete response in 14 and relapse in eight. In stage 1B patients stable disease was found in 12, progression in four, complete response in 7, and relapse in 8.

Stable disease was found in 9 of the stage 2A cases, progression in 3, complete response in 6, and relapse in 12. Stable disease was found in one of the stage 2B cases and progression in the other. Stable disease was present in stage 3 patients. Stable disease was determined in 4 of the stage 4 cases and progression in 1.

The treatment protocols given according to the disease stage are summarized in Table 2.

Treatment

At early stages all patients received adjuvant topical corticosteroid therapy, clobetasol 0.05% being generally employed. Topical corticosteroids were generally combined with phototherapy. In stage 1A, topical imiquimod was applied to one patient with limited lesions not responding to topical corticosteroids, and retinoid acid was applied to another. However, the treatments could not be tolerated due to irritation. Local radiotherapy was applied to early stage patients with limited resistant lesions. We used electron beam therapy with a usual total dose of 20 to 24 Gy administered in 10 to 12 fractions. Subtotal or total improvement was observed in all patients receiving radiotherapy. Phototherapy was applied to 87% of patients (PUVA to 33 and nbUVB to 54) as the first-line treatment option. Both phototherapy options were applied three times weekly. Complete response was observed in 51% of subjects receiving PUVA and in 56% of those receiving nbUVB. The mean relapse duration after treatment was 11.52 months. The response to treatment with nbUVB rates were high, particularly in patients with patch lesions, but relapse rates were also common. PUVA therapy was preferred in patients (33%) with thicker plaques and tumoral lesions and when no response was achieved with narrowband UVB therapy. Relapse was determined in 10 (19%) of the patients receiving narrowband UVB therapy and in 7 (21%) of those receiving PUVA therapy. We generally used maintenance treatment, especially in patients with frequent relapses, generalized disease (≥1B), and advanced stages. Once clearance of lesions has been achieved phototherapy with three time a week (30-40 sessions), we then applied maintenance treatment in the form of 6 sessions twice a week, 6 sessions once a week, and then 4 sessions in 2 weeks.

Twenty percent of patients received systemic therapy or chemotherapy. The most commonly employed systemic agents were interferon, bexarotene, and acitretin. These agents were generally administered concurrently with phototherapy. Bexarotene

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Table 3. Demographic characteristics and progression and mortality rates of mycosis fungoides in different countries

Authors	Country	Patient (n)	Sex (M:F)	Mean age (years)	Progression (%)	Mortality (%)
Agar *et al*. (6)	UK	1502	1.64	54.0	34.0	26.0
Talpur *et al*. (10)	USA	1263	1.11	55.3	28.5	8.1
Desai *et al*. (12)*	USA (Georgia)	393	1.11	53.6	21.9	19.6
Eklund *et al.* (2)*	Sweden	44	1.60	64.0	25.0	25.0
Doorn *et al.* (21)*	Netherland	309	1.73	61.0	25.0	15.0
Quaglino *et al*. (11)*	Italy	1422	1.72	59.0	29.7	-
Anadolu RY *et al*. (8)	Turkey	113	0.94	46.0	10.0	6.0
Baykal Selcuk *et al.**	Turkey	100	1.20	46.0	10.0	3.0

F: Female; M: Male
**Studies including only patients with mycosis fungoides

therapy was administered to 6 patients at a mean daily dosage of 300 mg/m^2 and was combined with nbUVB in 4 cases. The drug was discontinued due to lipid elevation in 2 patients and central hypothyroidism in another one. Disease control was achieved in 3 other patients, but could not be maintained due to lipid elevation in one patient, while treatment response was achieved in another but tumoral lesions subsequently developed. Interferon alpha therapy was administered to 13 patients and was used in combination with phototherapy. Acitretin and nbUVB therapy were applied to one patient. Stabilization of disease was achieved under treatment, but the lesions then increased after the first year of therapy.

CHOP protocol (cyclophosphamide, doxorubicin, vincristine, and prednisone) was applied in 4 cases of stage 4.

LDH elevation was present in 10 (10%) patients, eosinophilia in peripheral blood in 12 (12%), and total IgE elevation in 13 (13%). Sezary cells were found in peripheral smears in 2 patients. Large cell transformation was observed in three patients and additional malignancy in 11 patients. Hodgkin lymphoma was found in 2 of these patients, non-Hodgkin lymphoma in 1, invasive ductal carcinoma of the breast in 2, thyroid papillary carcinoma in 2, lung cancer in 2, colon cancer in 1, and hepatocellular carcinoma in 1. Thirty-seven patients were still surviving disease-free at the end of follow-up, while 10 had died, 3 of them due to the disease.

DISCUSSION

We evaluated the clinical characteristics and disease course of patients with MF in Turkey. Several mostly retrospective studies have been published on demographics and disease course of MF and Sezary syndrome (Table 3). In the literature the mean age at onset of the disease ranges between 54 and 64 (2,6). The mean age at onset in the present study and the other study from Turkey was 46 (8). Compared with other countries, we can conclude that Turkish patients had a younger age presentation. We think that patients are diagnosed at early stages of the disease due to early admission to dermatology clinics. The disease has been reported as more common in men in literature, which is in accordance with our study (1.2/1) (9,10).

MF is known as a slow progressive disease, and no decrease in the life span of stage 1A patients has been reported in most studies (2). In a multicenter retrospective study Quaglino *et al*. followed 1422 patients with MF and SS for an average of 14.5 years from diagnosis and reported that the majority of patients were in the early stage of the disease at time of diagnosis (stages 1A-2A, 87%). In the same study the risk of progression was shown to increase in more advanced stages. Progression levels in stage 1A, 1B, and ≥2A were 25%, 29%, and 40%, respectively. In the same study, 5-10 years life expectancy has also been shown to be decreased as the stage of disease increased (11). In a cohort study with 1502 patients, Agar *et al*. reported progression in 34% of subjects during follow-up and that 24% of patients died due to the disease (6). Ninety-two of the patients in our study had early-stage MF at the time of diagnosis. Disease progression regardless of stage was 10% in our study and the disease-specific mortality rates were 3%. Disease progression rates in the literature were reported between 10-34% (2,8,10-12). Death due to disease related conditions was considered as disease progression in Talpur *et al*. (10) and Agar *et al*. (6), but in our study and other abovementioned studies death due to disease was not classified as progression. In our study and the study by Anadolu *et al*. (8) from Turkey, disease progression was significantly lower. We may explain this by earlier diagnosis and treatment initiation in the Turkish population or due to do early treatment with phototherapy.

Cohort studies have shown an increased risk of a second primary lymphoma developing in patients with MF and SS, particularly Hodgkin lymphoma. In a retrospective analysis of the two cohort studies in the literature, the development of additional solid organ cancer rates was 8.9% and 11% (13). This rate was 11% in our study. Hodgkin lymphoma was found in 2 patients, non-Hodgkin lymphoma in 1, invasive ductal carcinoma of the breast in 2, thyroid papillary carcinoma in 2, lung cancer in 2, colon cancer in 1, and hepatocellular carcinoma in 1. Olsen *et al*. found an increase in secondary cancer development in patients with MF, but in contrast to other cohort studies they also included cancer cases diagnosed before MF diagnosis as secondary cancer (14). The reason for the increased risk of a second malignant neoplasm in patients with MF and SS is unknown. However, these secondary cancers are probably associated with the treatments of the disease. Alternatively, MF may have a common underlying environmental factor or a native tendency for the development of certain malignant neoplasms (13,15).

Large cell transformation in MF, diagnosed when large cells exceed 25% of the total lymphocyte count, is approximately 10-25%, depending on the stage (16). A retrospective analysis of 297 patients reported a level of large cell transformation of 1.4% in stage 1A and 2A disease, but 67% in 4B disease (17). Transformation was observed in 3 patients in our study. We attribute the lower rates in our research compared WITH the literature to the low number of advanced stage patients.

Phototherapy is a safe, effective, and well tolerated first-line treatment in patients with early stage of MF (1A-2A). Although the evidence for the effectiveness of narrowband UVB therapy is lower, it is thought to be as effective as PUVA in the initial treatment of early stage MF. It is preferred in patients with patch and thin lesions. PUVA therapy may be reserved for thick plaques and patients resistant to narrowband UVB therapy. It is recommended that PUVA or narrowband UVB treatment be administered three times per week until the lesions fully clear (18). Once remission has been achieved, there is no consensus regarding maintenance treatment. Avoiding maintenance therapy is recommended in the recently published EORTC (18). Sanchez *et al*. showed that maintenance therapy with PUVA did not prevent relapse in follow-up over approximately 28 months (19). Pavlotsky *et al*. reported that maintenance treatment in broadband and narrowband UVB therapy did not reduce relapse rates in cutaneous T-cell lymphoma (20). In the literature, the use of phototherapy in treatment of mycosis fungoides is significantly lower compared with our study. Quaglino *et al*. used phototherapy alone or with systemic agents in 54% of patients in stage 1, 31% in stage 2, 14% in stage 3, and 2.6% in stage 4 (11). Eklund *et al*. treated 70% of the patients with phototherapy as a first-line agent. They used PUVA twice a week for a total of 24-30 times: narrowband UVB was administered three times weekly with a similar number of treatments (2). Doorn *et al*. used phototherapy in 71% of the patients in stage 1 and 39% in stage 2 (21). Anadolu *et al*. used phototherapy in 91% of patients in early stages (<2B) and 33% in late stages (≥2B) (8). Phototherapy protocols were administered three times weekly, and mean duration of therapy was 21.50 months in early stages and 17.25 months in late stages. We used phototherapy alone or with systemic agents in 90% of stage 1A patients, 91% stage 1B, 97% stage 2A, and 100% stage 2B patients. We used maintenance treatment especially in patients with frequent relapses, generalized disease (≥1B) and advanced stages. We think that maintenance therapy could prevent progression of the disease. We had low progression rates despite the literature, which we can explain by early administration of phototherapy and maintenance therapy in the phototherapy protocol.

Our research was performed as a retrospective and single-center study. It also has various limitations, such as a low number of cases.

CONCLUSION

MF is a chronic disease with frequent relapses and disease progression despite treatments. Our study is a report from Turkey on demographic data and overall outcome of patients with MF. As expected, significant rates of stable disease and relapses were found in our patients. Unlike in the literature, mortality rates and disease progression were significantly lower. This chronic course of the disease and frequent relapses require new treatment regimens to achieve complete remission in patients. We observed an increased additional malignancy in our study. Further multi-center and prospective studies assessing prognostic factors, mortality rates, and responses to treatment in cases of MF in Turkey are needed.

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