Treatment of primary cutaneous lymphoma with reference to the latest therapeutic consensus of the Polish Lymphoma Research Group (PLRG)

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Abstract

Introduction: Primary cutaneous lymphomas are a heterogeneous collection of lymphoproliferative malignancies with a wide-ranging clinical picture, course and prognosis. Mycosis fungoides (MF) is the most common disease in this group. Mycosis fungoides, Sézary syndrome (SS) and lymphomatoid papulosis (LyP) are the most frequent primary cutaneous lymphomas treated in our department. Each disease requires a specific treatment, further adding complexity in this diverse group of pathologies.

Aim: To evaluate methods and results of treatment used in patients with primary cutaneous T-cell lymphoma (CTCL), treated in the Department of Dermatology, Venereology and Allergology, Medical University of Gdansk in 2007-2011, with reference to SLS (Skin Lymphoma Section) of PLRG (Polish Lymphoma Research Group).

Material and methods: One hundred sixty-three medical records of 68 hospitalized patients, with a suspected diagnosis of CTCL, were analyzed. The male-to-female ratio was 1 : 0.7, with the age range of 30-95 years.

Results: Twenty-four patients with MF were treated with topical corticosteroids, 21 with phototherapy, 6 with retinoid (acitretin), 2 with bexarotene (alone or in the combination with PUVA/UVB311). Methotrexate in low doses was used in 19 patients and interferon α in 4 patients. Radiotherapy was used in 7 cases and chemotherapy (2CdA or CHOP) was used in 11 cases.

Conclusions: It is difficult to evaluate the results of the treated group because of the short observation period. Not all methods of treatment suggested in the recommendations by the SChS PLRG and EORTC WHO were included.

Key words: cutaneous T-cell lymphomas, mycosis fungoides, Sézary syndrome.

Introduction

Primary cutaneous lymphomas constitute a heterogeneous group of pathologies that range from the indolent and benign to the aggressive and malignant ones. This article concerns three of them: mycosis fungoides (MF), Sézary syndrome (SS) and lymphomatoid papulosis (LyP). Mycosis fungoides is the most common primary cutaneous lymphoma, responsible for 50% of all primary cutaneous lymphomas, and will be the main focus of this article [1].

The MF has an indolent and chronic course; average 10-year survival rate of 97-98% for limited patch/plaque disease, 83% for generalized patch/plaque disease, 42% for tumor stage disease and 20% for lymph-node involvement (histopathologically documented) [1]. It mostly affects people in their 4th or 5th decade. The earliest stage presents as red-violet slowly growing, round or oval patches [2] resembling a tinea infection [3]. These lesions progress to plaques and eventually to tumors and internal organ metastases [2]. The lesions of a patch or plaque stage may arise anywhere on the body but show a predilection for non-sun-exposed areas, such as the buttocks, medial thighs, and breasts [4].

The clinical spectrum of MF is broad and it is not uncommon that all the lesions mentioned above occur simultaneously in patients. The TNM system is used to assess the clinical stage of the patients (Tables 1 and 2). The clinical stage, in turn, dictates the treatment, which is outlined in the guidelines (Table 4).

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Table 1. The clinical classification of cutaneous T-cell lymphomas [9]

T0 – Possible involvement (lesions clinically or histopathologically suspected)
T1 – < 10% involvement (patches, plaques or eczematous lesions concerning less than 10% of skin surface)
T2 – > 10% involvement (generalized patches, plaques or eczematous lesions, concerning more than 10% of skin surface)
T3 – Tumors (one or more)
T4 – Erythroderma
Nodular involvement – N
N0 – No involvement
N1 – Clinically involved nodes; pathology negative
N2 – No clinically enlarged nodes; pathology positive
N3 – Clinically involved nodes; pathology positive
Distant metastases – M
M0 – Without internal involvement
M1 – Internal involvement, with positive pathology confirmation
Blood – B
B0 – Without atypical blood cells – less than 5%
B1 – With atypical blood cells – more than 5%

Sézary syndrome is a rare disease characterized by a clinical triad: generalized erythema, generalized lymphadenopathy and Sézary/atypical cells in peripheral blood [5]. Like MF, its course is chronic, but with a more accelerated disease progression. Prognosis is generally poor with a median survival of 2-4 years [6, 7] and an average 5-year survival rate of 24% [1].

Table 2. TNM classification of cutaneous T-cell lymphomas [9]

Clinical stage	T (tumor)	N (lymph nodes)	M (metastases)
IA	1	0	0
IB	2	0	0
IIA	1, 2	1, 2	0
IIB	3	0-2	0
III	4	0-2	0
IVA	1-4	2, 3	0
IVB	1-4	0-3	1

Lymphomatoid papulosis is benign and requires no or minimal therapeutic intervention. However, its course is chronic and some research suggests that it may evolve into other lymphomas, as well as increasing the risk of developing other lymphoproliferative disorders [8].

Despite recent advances in treatment, such as retinoids, multi-agent chemotherapy, extracorporeal photopheresis, biological treatment (e.g. IFN-α), receptor-targeted cytotoxic fusion proteins, MF and SS remain incurable, with one exception: allogeneic hematopoietic cell transplantation (allo-HCT). Faced with this, rather than curing, treatment aims to ameliorate symptoms while minimizing therapeutic side-effects. The use of allo-HCT is discussed below.

Aim

The aim is to evaluate treatment results, with respect to short-term symptomatic improvement, in patients with primary cutaneous T-cell lymphoma (CTCL) treated in the Department of Dermatology, Venereology and Allergology, Medical University of Gdansk, in 2007-2011, with ref-

Table 3. Treatment results

Therapy	Number of patients	Stage	Remission of lesions [%] (our study)	Remission of lesions (other studies)	
				Complete remission [%]	Partial remission [%]
Glucocorticosteroids (topical)	24	IB-IVB	–	T1 60-65 [10] T2 25 [10]	T1 30 [10] T2 57 [10]
UVB 311	11	IA-IVA	91	54-92 [11, 12]	–
PUVA	12	IA-III	91.7	58-88 [11, 12]	–
Retinoids/Re-PUVA	6	IA-III	50	–	–
Bexarotene	2	IB-III	50	–	–
Methotrexate	19	IIA-IVB	53	T1 12 [13, 14]	T2 22 [13, 14]
Local radiotherapy	7	IIA	43	–	–
IFN-α	4	IIB-IVB	50	–	–
CHOP	4	IIB-IVB	50	–	–
2CdA	7	IIB-IVA	43	–	–

Table 4. Recommendations for treatment of mycosis fungoides (MF) and Sézary syndrome [15]

Clinical stage	First-line treatment	Second-line treatment
IA-IIA MF	• Topical corticosteroids (from the strongest group, 2-3 times per week for 3-4months) • PUVA (2-3 times per week) ± retinoids • UVB 2-3 times per week • Topically bexarotene • Topically carmustine • Localized radiotherapy • TSEB (patients with stage IB with slow progression)	• IFN-α monotherapy (3-5 MU daily) or + PUVA, retinoids • Bexarotene orally (300 mg/m^2) • Methotrexate (low doses 20-30 mg per week) (to 75 mg weekly) + ECP, PUVA and IFN-α • Vorinostat • Denileukin diftitox
IIB MF	• IFN-α (+ PUVA, retinoids, bexarotene, methotrexate) • TSEB or/and radiotherapy (6-10 weeks of therapy) • PUVA	• Bexarotene • Vorinostat • Romidepsin • Denileukin diftitox • Systemic chemotherapy • Monotherapy *p.o.*: chlorambucil, etoposide • Monotherapy *i.v.*: gemcitabine, liposomal doxorubicin • Bone marrow transplantation (in some patients)
III MF + Sézary syndrome III, IVA	• Extracorporeal photopheresis (in patients with Sézary syndrome) + oral steroids, IFN-α, bexarotene and methotrexate • IFN-α (3-5 MU everyday) + PUVA, retinoids, bexarotene and ECP methotrexate	• Bexarotene + ECP and IFN-α • Vorinostat • Denileukin diftitox • Romidepsin • Systemic chemotherapy • Monotherapy *p.o.*: chlorambucil, etoposide • Monotherapy *i.v.*: gemcitabine, liposomal doxorubicin • Polychemotherapy (CHOP, EPOCH, CC, FC, patterns of cytosine arabinoside) • Bone marrow transplantation
IVA, IVB MF	• TSEB and/or radiotherapy • Chemotherapy systemic • Monotherapy: gemcitabine, liposomal doxorubicin	• IFN-α (3-5 MU daily (+ PUVA) + retinoids, bexarotene and ECO • Systemic chemotherapy • Monotherapy *p.o.*: chlorambucil, etoposide • Monotherapy *i.v.*: gemcitabine, liposomal doxorubicin • Polychemotherapy (CHOP, EPOCH, CC, FC, patterns of cytosine arabinoside) • Low dose of methotrexate (+ steroids, ECP), PUVA • Denileukin diftitox • Vorinostat, romidepsin • Bone marrow transplantation

erence to the Skin Lymphoma Section (SLS) of the Polish Lymphoma Research Group (PLRG). How do these results compare to current research results? Are new and expensive drugs more effective than older and cheaper ones?

Material and methods

From a total of 3134 patients hospitalized in the Department of Dermatology, Venereology and Allergology, Medical University of Gdansk in 2007-2011, 68 patients with suspected primary cutaneous lymphomas were found; 32 MF patients, 2 LyP patients and 1 SS patient. The age range was 30-95 years with a male-female ratio of 1 : 0.7.

The patients were treated according to the Polish lymphoma group guidelines, using all available methods of treatment in Poland: topical glucocorticosteroids, local radiotherapy, UVB-311 (3-4 times per week), PUVA (3 times per week), bexarotene, methotrexate, interferon α (IFN-α), CHOP and 2CdA (2-chlorodeoxyadenosine).

Results were divided into two categories: complete remission (defined as equal to or more than 75% of dermal lesions), partial remission (defined as less than 75% regression of dermal lesions), or progression (defined as an increase in dermal lesions or/and internal organ involvements). Side effects were noted. Similar criteria are used in the evaluation of all primary cutaneous lymphomas.

Results

Topical glucocorticosteroids

Twenty-four patients with MF stage IB-IVB and 1 patient with LyP stage II were treated with topical glucocorticosteroids. It is not possible to assess the outcome

associated with their use as these were never used as an individual treatment.

UVB 311

Eleven patients with MF stage IA-IVA were treated with UVB 311. Ten patients (91%) achieved remission; 1 of them experienced ocular complications. One of the patients did not benefit from the treatment. The LyP patient was successfully treated with this method.

PUVA

The PUVA was used in 12 patients with MF stage IA-II. Remission was achieved in 11 cases (91.7%). One patient was lost in follow up.

Retinoids/Re-PUVA (retinoids + PUVA)

Six patients with MF stage IA-III were qualified for this treatment; 3 patients received retinoids alone, and 3 patients received Re-PUVA. One of the patients (33%) on retinoids alone achieved remission; the 2 remaining patients had progression of MF and died. Three patients treated with Re-PUVA responded with remission (2 patients – 67%) or progression (1 patient).

Bexarotene

Bexarotene (rexinoid) was used in 2 patients with MF stage IB-III. One of the patients was also treated with UVB311 and achieved remission, which lasted for 30 days; the relapse occurred during dose reduction. In this patient, the MF was confined to the skin (no lymph- node involvement or systemic progression) after 17 months of the disease. The patient is still under treatment. The other patient progressed rapidly and died after intensification with chemotherapy, despite only skin involvement (erythroderma, multiple tumors, lion's face). All patients suffered because of hypertrigliceridemia, hypercholesterolemia and hypothyroidism but there was no necessity to withdraw the treatment for these reasons.

Methotrexate

Low doses (15-25 mg weekly) of methotrexate were used in 19 patients with MF stage IIA-IVB. Ten patients (53%) achieved remission. In 3 patients, the treatment did not result in any changes. In 1 patient, only reduction of pruritus was achieved. Six patients progressed; one developed new tumors and Hodgkin's disease, one developed sepsis (neutropenia, ulcerations of the mucous membranes and skin lesions simulating Steven-Johnson Syndrome) but achieved remission after Total Skin Electron Beam (TSEB) therapy in the Department of Radiotherapy of the Medical University of Szczecin. The remaining patients suffered from complications and developed new tumors.

Local radiotherapy

Local radiotherapy was used in 7 patients with MF stage IIA. Three patients (50%) went into remission. One patient had progression of the disease and one was lost in follow up. Two patients suffered from complications: 1 of them developed ulcers and scars, the other 1 developed leucopenia.

Interferon-α

Four patients with MF stage IIB-IVB were qualified for treatment with IFN-α. Two (50%) achieved remission; one of them is still treated and the other one died after remission because of bladder cancer not CTCL. One patient survived for 6 months but was then lost in follow up. One patient developed agranulocytopenia and died.

Chemotherapy

Chemotherapy (CHOP) was given to 4 MF patients with stage IIB-IVB. Two patients (50%) went into remission and 2 had progression of the disease.

2CdA (Cladribine)

Seven patients with MF stage IIB- IVA were treated with 2CdA. Three (43%) of them achieved remission. In 1 patient treatment produced no effect. The remaining 3 patients suffered from complications (sepsis, agranulocytosis).

Lymphomatoid papulosis

One of the 2 patients was treated with the "watch and wait" method. This patient stage IA went into remission. The other patient, stage II, was treated with UVB-311 and topical steroids. This patient also achieved remission.

Sézary syndrome

In 1 patient with Sézary syndrome, stage IVA, 2CdA was used. Remission was achieved.

Discussion

The treatment of MF optimally uses a multidisciplinary approach. As a cure still does not exist, the best current treatment should induce a long-lasting regression, with no or little side effects. Do "new" and, most often, more expensive treatments (denileukin diftitox, romidepsin, vorinostat etc.) achieve this to a greater degree than the "old" ones (phototherapy, topical steroids, methotrexate etc.)?

Three "types" of phototherapy were in use in our patients: PUVA, UVB-311 and Re-PUVA. Treatment with PUVA three times a week led to remission in 91.7% of patients with MF stage IA-III. UVB-311 (3-4 times a week) led to remission in 91% of patients with MF stage IA-IVA.

The efficacy of Re-PUVA was lower; 50% in patients with MF stage IA-III. Other studies show a lower success rate of 58-88% for PUVA and 54-92% for UVB-311 [11, 12].

According to the guidelines, methotrexate is recommended in all stages of MF. It was used in 19 of our patients (MF stage IIA-IVB) with a success rate of 53%. Studies have shown that 20-75 mg methotrexate per week, given every 12 h to patients in T2, resulted in complete remission in 12% of patients and partial remission in 22% of patients, with an asymptomatic post-treatment period lasting on average for 15 months [13, 14].

Local radiotherapy effectively targets changes in the patch, infiltrative, and tumor stages of MF, as well as relapses and progression of the disease. Seven patients, with MF stage IIA, underwent local radiotherapy, showing an efficacy of 43%.

It is not possible to evaluate the efficacy of topical glucocorticosteroids, as they were infrequently used as a monotherapy, but rather in combination with other treatments.

The remaining treatments are difficult to evaluate due to their limited use. In the case of poly-chemotherapy, such as CHOP and purine analogues, such as 2CdA (cladribine), the reasons for their limited use are clear. These treatments are highly toxic; associated with a high risk of immunosuppression, myelosuppression and, consequently, increased susceptibility to infections. Furthermore, research has shown that the use of chemotherapy in patients with more advanced disease (stages IIB-IVB) does not lead to prolongation of survival time, nor does it halt disease progression [16]. For these reasons, their role is reserved for use when all other treatment options have been exhausted, or in patients with lymphadenopathy and/or organ involvement who need urgent reduction in tumor size [17].

In our group of 4 patients, CHOP was given to patients who, according to the guidelines, should have received milder treatment, for example, photopheresis (not available in Poland for CTCL patients), vorinostat, denileukin, diftitox etc. However, this being the only option, it was given to these patients.

Our patients receiving 2CdA should ideally have been given less toxic drugs such as gemcitabine or liposomal doxorubicin. However, this requires close collaboration with hematologists and oncologists (the use of IFN-α also requires such collaboration). Remission (using 2CdA) was achieved in 43% of 7 patients with MF IIB-IVA. However, follow-up revealed the remissions to be short-lasting (only a few weeks) in most of the patients.

The limited use of IFN-α and bexarotene is attributed to limited funding and/or subsidization. Other drugs, such as carmustine, vorinostat, denileukin diftitox, romidepsin and monochemotherapy (gemcitabine or liposomal doxorubicine) were not used whatsoever in our patients, for the same reasons. Interferon-α, despite it being a first line therapy in MF patients stage IIB-IVA, is only refunded for treatment in oncological departments. According to literature, IFN-α shows significant efficacy in virtually all stages of MF [18]. In our sample, 2 out of 4 patients given IFN-α, went into remission.

Bexarotene, a 2nd line drug in all stages of MF, has fallen victim to the same unfortunate circumstances. It was only used in 2 of our patients, achieving an efficacy in 50%. The limited use of bexarotene is regretful considering the results of Abbot *et al.*, who demonstrated the effectiveness of this synthetic retinoid in more than half of the treated patients, in all stages of the disease [19]. Bexarotene is currently recommended in stages without generalized progression, in which its effectiveness is the highest [20].

The TSEB therapy and photopheresis are two more examples of "new" treatments that were not used in our patients, because no such treatment is available in our clinical center. The lack of TSEB is perhaps the most regrettable, as it has shown high efficiency in the early stages of MF [18, 21, 22]. Additionally, TSEB results in rapid and sustained remission in approximately 97% of patients, with a high safety profile, both immediately after and during the long follow-up after treatment [23]. Photopheresis is a 1st line treatment option in MF stage III, as a single agent, or as part of a combined therapy – with PUVA or IFN-α – with high remission rates [1].

Allo-HCT is emerging as a new and promising treatment and cure for MF and SS. At the moment, however, its use is strongly limited as it only applies to patients in good general condition. Considering the epidemiology of MF, most patients are in their 50's or 60's with many comorbidities. Therefore, only a small number of patients qualify for allo-HCT. According to Duarte *et al.* [24], patients treated with allo-HCT show an overall-survival of 66% at 1 year and 54% at 3 years. The same research also showed that survival is strongly correlated with the donor type, disease phase and type of conditioning. Additionally, they reported that, in some cases, relapses were successfully treated with donor lymphocyte infusions.

Most primary cutaneous lymphomas are indolent neoplasms showing great symptomatic diversity. Aggravating symptoms, such as pruritus and disfiguring skin lesions, severely affect the quality of life. Dysfunction of the immunological system, in late stages, result in infections and secondary malignancies, quite often intensified by too early and/or too "strong" therapeutic interventions, such as polychemotherapy. Consequently, most patients die from infectious problems secondary to immunosuppressive treatment, rather than from the lymphoma itself. It must be remembered that most patients with primary cutaneous lymphomas are elderly and suffer from comorbidities, such as hypertension, diabetes etc. These factors adversely influence the side effects of treatment. For this reason, skin-directed therapy (topical corticosteroids and phototherapy) should always be the primary therapeutic option. "New" biological treat-

ments (vorinostat, romidepsin, denileukin diftitox) and "new" (in Poland) procedures (photopheresis), have a milder side effect profile than the classical treatments, and should be pushed hard for introduction into Polish reality – saving our CTCL patients. Because there is no curative treatment, the goal should be to achieve long-lasting remission with medicaments or procedures, which are safe and have low toxicity. There is a lack of high-quality randomized clinical trials evaluating the treatment of primary cutaneous lymphomas. It is therefore necessary to learn from the European and world therapeutic consensus, and to proceed with common sense. The central principle of treatment should be to heal and not to hurt.

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