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Original article

Treatment of patients with primary cutaneous lymphomas – real-life data

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Background. Primary cutaneous lymphomas (PCL) comprise a heterogeneous group of neoplasms of mature lymphocytes with skin tropism. Although, by definition, these lymphomas are restricted to the skin at the time of diagnosis, during the course of the disease it may involve also lymph nodes and visceral organs. A close cooperation between a dermatologist and oncologist is required to ensure proper treatment. We present in a real-life data on treatment of patients with PCL between dermatology and oncology department.

Material and methods. 104 patients were registered in a joined database of Oncology Department of Oncology Centre in Bydgoszcz and Dermatology Department of Medical University in Toruń between 2007 and 2017. Due to different clinical and prognostic features data from MF/SS (44 patients), non-MF/SS CTCLs and CBCLs were presented separately.

Results. Median overall survival for patients with MF/SS was 76.7 months. Median follow-up time was 5 years.

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Key words: cutaneous lymphoma, follow-up data, mycosis fungoides, daily practice

Introduction

Primary cutaneous lymphomas (PCL) are rare extranodal non-Hodgkin lymphomas, 75% of them are derived from T lymphocytes (cutaneous T-cell lymphomas, CTCL) and 25% from B lymphocytes (cutaneous B-cell lymphomas, CBCL) [1–3].

CBCLs are divided into 3 subgroups: primary cutaneous follicle centre lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT) [1–3]. CTCLs comprise a group of distinct entities with significantly varied clinical, histological and immunophenotypic features and prognoses.

The diagnosis and classification of PCL is based on histological assessment and immunohistochemical staining of an skin biopsy specimen. A prompt diagnosis is often difficult due to PCLs relative rarity and unspecific clinical presentations.

Mycosis fungoides (MF) and its leukemic phase, Sézary Syndrome (SS), is the most predominant subtype of CTCL ~53% [1–4]. MF can mimic different skin conditions, such as eczema, atopic dermatitis, psoriasis, and even other cutaneous lymphomas.

Histological findings are often unspecific and overlap with those of other inflammatory or non-neoplastic diseases so empirical treatment e.g. with topical steroids may hamper the diagnosis. MF has usually an indolent course and a good prognosis. Early-stage MF can be successfully managed by skin-directed therapy, advanced stages of MF and SS require systemic treatment modalities [4].

There is a relative scarcity of data regarding the treatment options of advanced stages CTCLs from non-dermatological units in Poland [5–8]. The aim of this paper is to present real-life clinical data on therapeutic collaboration between dermatological and oncological department. The data have been prepared within the framework of the Polish Lymphoma Research Group.

Methods

104 patients were diagnosed with PCL between 2007 and 2017 in Oncology Centre in Bydgoszcz and Dermatological Department of Medical University in Toruń.

The diagnosis of PCL was made when the clinical features were consistent with histological review and additional tests such as immunophenotyping. The PCL diagnosis was confirmed when lymphomatous infiltration was limited to the skin without any extracutaneous primary lesions found at the moment of diagnosis and subsequent 6 months of follow-up.

Initially, the patients with early stages of PCL were treated with skin-directed therapies such as PUVA or topical steroids. The first line of systemic therapy for advanced stages of PCL was either low-dose interferon alfa 2 beta (subcutaneous injection, 3 million units, 3 times per week) or low-dose methotrexate (orally, 20 mg per week). Subsequent treatment options varied widely depending on the patient's condition and drug availability.

Current paper focuses on the retrospective analysis of clinical data of unselected population of 44 patients diagnosed with MF/SS treated in years 2007–2013. 48 patients with MF/SS who were diagnosed after July 2014 were excluded from the analysis due to participation in the observational clinical trial (NCT 0232365). Due to distinct clinical features and prognosis, patients with non-MF/SS CTCLs and CBCLs are presented separately.

Statistical analysis comprised the calculation of overall survival, patients characteristics, previously applied treatment and coexisting comorbidities.

Results

The number of visits of the patients referred to the Dermatology Department in 2007–2017 with various dermatoses to confirm a suspicion of PCL are presented in table I. A confirmatory diagnosis of PCL was made in 104 patients. The data from 2006–2009 are not available due to technical reasons. The number of confirmed diagnosis of various types of PCL in 2007–2017 with ratio of non-MF PCLs to MF is presented in table II.

MF/SS was diagnosed in 92 patients (88.46% of PCLs); 44 subsequent patients treated in 2007–2013 were included into the analysis. The median follow-up time was 5 years.

Table II. The data from Oncologic Centre – the number of new patients with confirmed skin lymphoma. The proportion between more frequent type: MF (mycosis fungoides), SS (Sezary Syndrome) versus other types of skin lymphoma

Year	Number of new patients with confirmed skin lymphoma	Other type skin lymphoma/ /MF+SS
2007	6	1/5
2008	4	0/4
2009	5	0/5
2010	8	1/7
2011	14	2/12
2012	3	1/2
2013	15	2/13
2014	8	3/4
2015	16	2/14
2016	12	0/12
2017	13	0/12
All	104	12/92

These data comprise the whole 10 years period 2007–2017. Other skin lymphomas are represented both by B cell and T cell lymphoma: the details are shown in table III and IV. The number of diagnosed cutaneous lymphomas with respect to cases of dermatosis with a similar clinical picture (table I) was assessed to emphasise the scale of diagnostic needs in this area in everyday practice

Table I. The number of visits in a dermatologic department caused by dermatoses or inflammatory dermatoses in relation to the number of visits of the patients with CTCL between 2010 and 2017

Year	Allergic Contact dermatitis L23	Atopic skin dermatitis L20	Eczema L30	Parapsoriasis L41	Papulosquamous disorders L44	Contact dermatitis L24	All inflammatory dermatoses MF like
2010	441	147	203	29	16	46	246
2011	489	158	139	61	6	125	198
2012	529	98	251	48	16	116	186
2013	575	40	288	69	14	164	212
2014	636	63	323	92	21	137	190
2015	796	70	477	115	36	98	219
2016	1263	187	804	137	20	115	184
2017	1489	193	997	160	30	109	140

The data from 2006 to 2009 are not available due to technical reasons. The growing number of civilizational skin diseases resulting from this visits and diagnostic needs draws special attention

Table III. Clinical data of 44 MF/SS who started the treatment between 2007 to 2013, and have been follow up minimum 5 years

Woman	Men	Age <60	Age >61	MF primary	SS primary	Stage IIB	Stage III	A/B1/not known	B2
16	28	20	24	41	3	8	36	22/16/6	3

A – blood cytometry without any abnormalities, B1 – not clinically significant number of pathologic lymphocytes, B2 – significant number of pathologic lymphocyte

MF/SS was more prevalent in men (63%) and patients above 61 years (54%). Most patients (81.8%) were in stage III at the moment of the initiation of systemic treatment. The summary of clinical characteristics of the patients with MF/SS is presented in table III. The frequency of comorbidities and other coexisting dermatoses is shown in table IV. Alcohol use disorder was retrospectively diagnosed in 22.72% of all MF/SS patients. The summary of data regarding the first line of systemic treatment is presented in table V.

Interferon (INF) as the first-line treatment was used in 36 patients, methotrexate (MTX) was used in 8 patients. The median duration of treatment with interferon was 14 months and the median duration of treatment with methotrexate was 10 months. 23 patients received 2 lines of systemic therapy,

Table IV. The frequency of other skin diseases and comorbidities

Atopic dermatitis	Skin allergy not specified	Parapsoriasis	Other skin diseases	Cardio-vascular comorbidities	Diabetes	ZZA	Depression
44	27	17	40	24	23	10	17

ZZA – alcohol

Table V. The types of treatment and response

Interferon I line/ /months of therapy	Interferon RR	Methotrexate I line/ /months of therapy-medium value	Methotrexate RR	SAE-Interferon	SAE-Methotrexate
36 pts/3–120 Median: 14	CR–8, PR–28	8 pts/4–96 Median: 10	CR–2, PR–6	1 depression	1 infarctus

Death	Alive patients	Median OS	Pts treated to progression without interval/median OS	Pts treated to PR and after progression/median OS	Patients post SCT/ /with CR
14	30	76.7 months	23/4–144 mts, median: 74.3 mts	21/6–144 mts, median: 79.1 mts	4/4

pts – patients, SCT – stem cell transplantation

Table VI. CBCL and non MF/SS CTCL treatment details

CBCL type/gender	I line	II line	Maintenance	Observation only/ /medium number of visits per years	Efficacy/ /I line	Relapse	Time to II line
PCFCL/W	COP	No	No	No/7	CR	No	n.a
PCFCL/M	No	No	No	Yes/3	n.a	n.a	n.a
PCMZL/K	AC due to breast cancer	No	No	No/12	CR	No	n.a
PCDLBCL/W	R-CHOP	No	No	No/9	CR	No	n.a
FL/W	R-CVP	No	No	No/6	CR	No	n.a
FL/W	R-CVP	No	Yes	No/5	CR	No	n.a
DLBCL/W	R-CHOP mini	No	No	No/9	SD	Yes	n.a
LYP CD30+/W	MTX	n.a	No	No/12	CR	No	n.a
PCALCL ALK + CD 30+/M	Surgery	n.a	No	Yes/3	CR	No	n.a
PCALCL ALK–CD30+/W	MTX/surgery	ICE + SCT	No	n.a/12	CR	Yes	15
PCALCL ALK+ CD 30+/M	MTX	MTX	No	n.a/6	CR	No	n.a
LYP CD 30–/W	MTX/Interferon	Bexarotene	No	No/12	SD	Yes	56

CR – complete remission, PR – partial remission, SD – stabilisation, PD – progression, W – woman, M – man, PCFCL – primary cutaneous follicle centre lymphoma, PCMZL – primary cutaneous marginal zone lymphoma, PCDLBCL LT – primary cutaneous diffuse large B-cell lymphoma (leg type), PCALCL – primary cutaneous anaplastic large cel lymphoma, LYP – lymphomatoid papulosis, n.a – not applicable

15 patients – 3 lines and 15 patients – more than 3 lines (9 pts – 4 lines, 5 pts – 5 lines, 1 pt – 6 lines). The chemotherapy regimens used for relapsed or refractory disease beyond the second-line therapy were as follows: gemcytabine (10 pts), liposomal doxorubicin (11 pts), cytarabine (4 pts), pralatrexate (1 pt), bexarotene (8 pts).

Stem cell transplant (SCT) was performed in 4 patients after achieving remission after the use of romidepsin as an induction therapy (3 pts – allogeneic SCT, 1 pt – allogeneic SCT). 2 patients participated in Millennium clinical trial and received alisertib and pralatrexate. Overall survival data is presented in table VI.

There were 7 patients with CBCL. Patients with CBCL received rituximab-containing chemotherapy regimens. 1 patient with synchronic and breast cancer was treated with AC chemotherapy with subsequent breast-conserving surgery followed by radiotherapy.

5 patients have had a long-term remission. 2 patients with CBCLS died: 90 year old man due to a cardiovascular disease and 78-year old woman due to the disease progression; patients were diagnosed with lymphomatoid papulosis (CD30+ – 1 pts, CD30– – 1 pts) and 3 patients were diagnosed with primary cutaneous anaplastic large cell lymphoma CD30+ (ALK– – 1 pt, ALK+ – 2 pts).

A patient with PCALCL ALK+ received a complete remission after polychemotherapy and treatment was consolidated by allogeneic HCT. A patient with LyP CD30+, resistant to initial MTX and INF treatment, received bexarotene treatment with long-lasting partial remission despite the need for a significant dose reduction of bexarotene. Tables VI and VII presents clinical course and survival data CBCLS and non MF/SS lymphoma.

Discussion

CTCLs comprise a group of heterogeneous lymphomas with a varied clinical behaviour. Most CBCLs are indolent lymphomas that infrequently infiltrate extracutaneous sites, have a good prognosis and may be effectively managed with locally targeted therapies. The advanced stages of CBCLs require immunochemotherapy as other nodal non-Hodgkin lymphomas. The data presented in this paper regarding CBCLs and its clinical features are consistent with other reports [1, 2]. CTCL is the most dominant type of PCL. Most dominant subtypes of CTCL were MF/SS (44 pts), CD30+-lymphomas; other subtypes like PCALCL and LyP were rare (5 pts). Low-dose methotrexate is a frequent first line therapy for multifocal PCALCL with good clinical results and the rate of complete remission near 40% [9].

Two patients were MTX-resistant and required subsequent therapy. 1 patient was successfully managed by the surgical removal of a skin lesion.

Although MF is the most common type of PCL, the reports regarding treatment options is relatively sparse. A broad spec-

Table VII. Clinical data and overall survival in CBCL and patients with non MF/SS

Type PCL	Sex	Age	First visit	Other skin diseases	Comorbidities	Stage	Alive yes or no/OS	Date of death
PCFCL	W	59	V 2007	Any	(–)	T4N0M0 Symptoms B+	Yes/141 months	n.a
PCFCL	M	90	IV 2014	Any	Dementia	T4N1M0	No/14 months	June 2015
PCMZL	W	64	VII 2013	Any	Breast cancer	T3N0M0	Yes/67 months	n.a
PCDLBCL leg type	W	49	IX 2014	Any	Diabetes	I X A	Yes/54 months	n.a
PCFCL	W	59	X 2015	Any	(–)	T4N0M0	Yes/39 months	n.a
PCFCL	W	70	VII 2014	Any	Hypertension	T4N0M0	Yes/52 months	n.a
PCDLBCL leg type	W	78	III 2015	Any	Diabetes, hypretension	T4N1M0	No/8 months	October 2015
LYP CD30+	W	64	III 2010	Hypertension	Atopic dermatitis	T3N0M0	Yes/106 months	n.a
PCALCL ALK+ CD 30+	M	44	V 2011	Any	(–)	T1N0M0	Yes/91 months	n.a
PCALCL ALK– CD 30+	W	47	XI 2011	Any	(–)	T3N0M0	Yes/85 months	n.a
PCALCL AKL+CD30+	M	39	II 2012	Any	(–)	T3N0M0	Yes/82 months	n.a
LYP CD30–	W	72	I 2013	Coronary disease	Skin allergy not specified	T4N1M0	Yes/72 months	n.a

W – woman, M – man, PCFCL – primary cutaneous follicle centre lymphoma, PCMZL – primary cutaneous marginal zone lymphoma, PCDLBCL LT – primary cutaneous diffuse large B-cell lymphoma (leg type), OS – overall survival, PCALCL – primary cutaneous anaplastic large cell lymphoma, LYP – lymphomatoid papulosis, n.a – not applicable

trum of clinical features of MF may be initially missed and thus adequate therapeutic measures delayed.

Another problem regarding the treatment of MF is the limited access to novel drugs due to reimbursement decisions. Currently in Poland there is no access to treatment options like romidepsin and other HDAC inhibitors, denileukin diftitox, pegylated liposomal doxorubicin or extracorporeal photopheresis. [13–16]. For an early stage MF confined to the skin, the therapeutic concept is to control symptoms by use of skin-directed therapies e.g. topical agents such as corticosteroids, mechlorethamine, carmustine, retinoids, phototherapy, superficial radiotherapy, and total skin electron beam therapy. Due to chronic and recurrent nature of MF, in advanced stages, repeated systemic treatment are necessary for disease control [19, 20]. Possible systemic treatment options are: bexarotene, interferon-α, histone deacetylase inhibitors, denileukin diftitox, chemotherapy [13, 19, 21].

Single-agent chemotherapies with a high overall response rate (ORR) are as follows [13–16, 21]: pegylated liposomal doxorubicin (ORR = 88% in stage IA–IV 88%), gemcitabine (ORR = 70% in stage IIB–III), fludarabine (ORR = 55% in stage IIA–IV) [17]. Fludarabine can be substituted by cytarabine because of its favourable safety profile – it was used in 4 patients as salvage therapy. Allogeneic HCT is currently the curative treatment option advanced and resistant MF/SS for young and otherwise healthy patients [19, 21]. The median overall survival for advanced stage MF reported in literature (IIB–IVA) is 60 months [17, 21, 23]. In this study median OS was 75 months.

The aim of this analysis was to confront the treatment options recommended in professional guidelines with every-day practice. In the author's opinion, a limited access to the novel drugs and a small number of clinical trials in Poland make many of proposed treatment modalities a not viable option for the Polish population [17, 24]. Because of the rarity and a varied natural course of the MF, ranging from indolent to highly aggressive, the close cooperation between a dermatologist and an oncologist in important. In Poland there are formal limitations regarding which kind of treatment can be applied by a specific specialist [25]. Recently, radiotherapy has been more frequently used than in the past, but extracorporeal photopheresis is still not available because of reimbursement issues (the exception is GVHD after allo-SCT) [20].

The debate concerning the best way of treatment of these rare lymphoprolfierative disorders is necessary. Researchers hope that increased understanding of the pathogenesis of cutaneous lymphomas with identification of important molecular markers will lead to the development of new targeted therapies and a better effectiveness of the treatment [26].

Conflict of interests: none declared

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References

1. Bradford PT, Devesa SS, Anderson WF et al. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood.* 2009; 113 (21).
2. Imam MH, Shenoy PJ, Flowers CR et al. Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. *Leuk Lymphoma*. 2013; 54 (4): 752–759.
3. Quaglino P, Maule M, Prince HM 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.* 2019; 30 (3): 494.
4. Olek-Hrab K, Silny W. Diagnostics in mycosis fungoides and Sezary syndrome. *Rep Pract Oncol Radiother.* 2013;19 (2): 72–76.
5. Olek-Hrab K, Maj J, Chmielowska E et al. Methotrexate in the treatment of mycosis fungoides – a multicenter observational study in 79 patients. *Eur Rev Med Pharmacol Sci.* 2018; 22 (11): 3586–3594.
6. Chmielowska E, Studziński M, Giebel S et al. Follow-up of patients with mycosis fungoides after interferon α2b treatment failure. *Postępy Dermatol Alergol*. 2015; 32 (2): 19.
7. Chmielowska E, Grzanka A, Krause A et al. Safety and efficacy of interferon-alfa2b (IFN) in the treatment of patients with mycosis fungoides. *Onkol. Prak. Klin.* 2011; 7 (6): 301–310.
8. Adamska K, Olek-Hrab K, Misterska M et al. Mycosis fungoides: therapeutic difficulties. *Postępy Dermatol Alergol.* 2015; 32 (5): 404–408.
9. Sokołowska-Wojdyło M, Lech-Marańda E, Placek W et al. Leczenie pierwotnych chłoniaków skóry. Rekomendacje Sekcji Chłoniaków Skóry Polskiej Badawczej Grupy Chłoniaków. *Onkol Prakt Klin*. 2010; 6: 29–47.
10. Geller S, Myskowski PL, Pulitzer M et al. Cutaneous T-cell lymphoma (CTCL), rare subtypes: five case presentations and review of the literature. *Chin Clin Oncol*. 2018. [Epub ahead of print]
11. Prince HM, Kim YH, Horwitz SM, ALCANZA study group. Brentuximab vedotinor physician choice in CD30 positive cutaneous T cel lymphoma; an international open-label randomized, phase 3 multicentre trial. *Lancet.* 2017; 390 (10094) 555–566.
12. Sokołowska -Wojdyło M, Walewski J, Jędrzejczk WW et al. Polish expert's opinion concerning brentuximab vedotin in the treatmentof patients with primary cutaneous lymphomas with CD30 expression. *Hematologia*. 2018; 9: 83–89.
13. Prince HM, Whittaker S, Hopper T. How I treat mycosis fungoides and Sézary syndrome. *Blood.* 2009;114 (20): 4337–4353.
14. Ross C, Tingsgaard P, Jorgensen H et al. Interferon treatment of cutaneous T-cell lymphoma. *Eur J Haematol.* 1993; 51: 63–72.
15. Aviles A, Nambo MJ, Neri N et al. Interferon and low dose methotrexate improve outcome in refractory mycosis fungoides/Sezary syndrome. *Cancer Biother Radiopharmaceut*. 2007; 22: 836–840.
16. Zinzani PL, Balivia G, Magagnoli M. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma;experience in 44 patients. *J Clin Oncol.* 2000; 18: 2603–2606.
17. Trautinger F, Eder J, Assaf C et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2017. *Eur J Cancer.* 2017; 77: 57–74.
18. Sokołowska-Wojdyło M, Florek A, Zaucha JM et al. Polish Lymphoma Research Group Experience with Bexarotene in the treatment of cutaneous T-cell lymphoma. *Am J Ther*. 2016; 23 (3): e749–756.
19. Querfeld C, Zain J, Rosen St. Primary cutaneous T-cell lymphomas: mycosis Fungoides and Sezary syndrome. *Cancer Treat Res.* 2019; 176: 225–248.
20. Piotrowski T, Fundowicz M, Pawlaczyk M. Total skin electron beam therapy with rotary dual technique as palliative treatment for mycosis Fungoides. *In Vivo*. 2018; 32 (3): 517–522.
21. Whittaker SJ, Foss FM. Efficacy and tolerability of currently available therapies for the mycosis fungoides and Sezary syndrome variants of cutaneous T-cell lymphoma. *Cancer Treat Rev.* 2007; 33 (2): 146–160.
22. Martinez-Escala ME, Kantor RW, Cices A, et al. CD8+ mycosis fungoides: a low-grade lymphoproliferative disorder. *J Am Acad Dermatol*. 2017; 77: 489–496.
23. Jawed SI, Myskowski PL, Horwitz S et al. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part II. Prognosis, management, and future directions. *J Am Acad Dermatol.* 2014; 70 (2): 223.e1–17.

24. Foss FM, Girardi M. Mycosis Fungoides and Sezary syndrome. *Hematol Oncol Clin North Am*. 2017; 31 (2): 297–231.
25. Berg S, Villasenor-Park J, Haun P et al Multidisciplinary management of mycosis Fungoides/Sézary syndrome. *Curr Hematol Malig Rep*. 2017; 12 (3): 234–243.
26. Adult treatment editorial board. Mycosis Fungoides (including Sézary syndrome) treatment (PDQ®): Patient version. PDQ cancer information summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002–2017, Sep 7.